



Statistical Analysis Plan

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A 52-week, double-blind, randomised, multi-centre, phase III, parallel-group study in patients 12 years and older with asthma, evaluating the efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg ‘as needed’ compared with Pulmicort (budesonide) Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg ‘as needed’



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Study Statistician


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08 SEP 2017
Date

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Global Product Statistician



Rosa Lamarca

8th September 2017

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-5	Asthma Control Questionnaire 5-item version
AE	Adverse event
ANCOVA	Analysis of covariance
AQLQ(S)	Asthma Quality of Life Questionnaire (Standardised version)
ATC	Anatomical therapeutic chemical
BID	Twice daily
CI	Confidence Interval
CSR	Clinical study report
DAE	Adverse event leading to discontinuation
DBL	Database lock
(e)CRF	(Electronic) Case report form
EoT	End of Treatment
ERS	European Respiratory Society
EU	European Union
EQ-5D-5L	EuroQol Quality of Life Questionnaire
FAS	Full analysis set
FCS	Fully conditional specification
FDA	(United States) Food and Drug Administration
FEV ₁	Forced expiratory volume in one second
FVC	Forced vital capacity
GCS	Glucocorticosteroid
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
HRU	Healthcare resource use
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICS	Inhaled (gluco)corticosteroid
IP	Investigational product
IVRS/IWRS	Interactive voice/web response system
J2R	Jump to reference
LTRA	Leukotriene antagonist

Abbreviation or special term	Explanation
MAR	Missing at random
NICE	National institute of clinical excellence
MID	Minimal important difference
MMRM	Mixed model repeated measures
MNAR	Missing not at random
OAE	Other significant adverse event
PN	Predicted normal
PT	Preferred Term
QA	Quality Assurance
SABA	Short-acting β -agonist
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subject characteristics
SOC	System Organ Class
TUM	Turbuhaler usage monitor
VAS	Visual Analogue Scale
vs	versus

AMENDMENT HISTORY

Date	Brief description of change
6 February 2017	AstraZeneca comments incorporated. The primary objective revised from demonstrating superiority to demonstrating non-inferiority (to be consistent with revised primary objective per study protocol Amendment 4)
8 March 2017	Decision to exclude 12 randomised patients from SYGMA2 study site 5702 (Poland) will be excluded from the Full Analysis set and the Safety analysis set due to significant deviations. The deviations were mainly relating to unavailability, discrepancies and poor quality of source data which question the validity and integrity of the trial data generated from this site.
8 March 2017	Decision to exclude all randomised patients in France in the non-inferiority test due to Ethic Committee rejection of CSP amendment 4 in France.
24 th March 2017	Version 1.2 Updated by Phastar pre-BDR1
13 th April 2017	Decision to exclude 1 randomised patient from study site 2612 (Germany) that was randomised in error from Full Analysis Set and Safety Analysis Set. Due to the subject age, local ethics committee decided data of this patient cannot be used for the analysis.
1 st June 2017	Version 1.3 Updated by Phastar after BDR1 CRM
21 st June 2017	Version 1.4 Updated by Phastar after AZ review
18 th August 2017	Version 1.5 Updated by Phastar post BDR2 for AZ review
6 th September 2017	Version 2 Updated by Phastar after AZ review.

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Outcome Measure:
To demonstrate that Symbicort Turbuhaler 160/4.5 µg ‘as needed’ is non-inferior to Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg ‘as needed’.	Annual severe asthma exacerbation rate

1.1.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To estimate the difference in efficacy between Symbicort Turbuhaler 160/4.5 µg ‘as needed’ and Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg ‘as needed’	Secondary variables <ul style="list-style-type: none"> • Time to first severe asthma exacerbation • Change from baseline in pre-dose forced expiratory volume in one second (FEV₁) • Time to study specific asthma related discontinuation • Change from baseline in ‘as needed’ use • Change from baseline in percent of ‘as needed’-free days • Percentage of controller use days • Change from baseline in Asthma Control Questionnaire—5-item version (ACQ-5) score • Change from baseline in Asthma Quality of Life Questionnaire Standardised Version (AQLQ(S)) score

1.1.3 Safety objective

Safety Objective:	Outcome Measure:
To compare the safety of Symbicort Turbuhaler 160/4.5 µg ‘as needed’ with that of Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg ‘as needed’	Adverse events (nature, incidence and severity); pulse, blood pressure and physical examination

1.1.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To compare health care resource utilization, indirect resource use and health related status associated with hospital admissions, health care visits and days lost from work/ school between treatment arms	<ul style="list-style-type: none"> • EuroQol five dimensional 5-level questionnaire (EQ-5D-5L) • Health Economics Questionnaire for resource utilisation

1.2 Study design

This is a 52-week, double-blind, randomised, multi-centre, parallel-group, phase III study in patients 12 years and older with asthma, evaluating the efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg ‘as needed’ compared with Pulmicort (budesonide) Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg ‘as needed’.

Figure 1 illustrates the flow of patients through the study from enrolment to study end. Patients will begin with a 2 to 4 week run-in period to collect baseline data and to ensure that they are in need of Global Initiative for Asthma (GINA) step 2 treatment. Patients will then be randomised to one of the two treatment groups described above and continue on the study for 52 weeks. Patients will receive a final follow-up telephone call to check for adverse events (AE).

Table 1 describes the assessments to be performed at each of the scheduled study visits.

Figure 1 Study flow chart

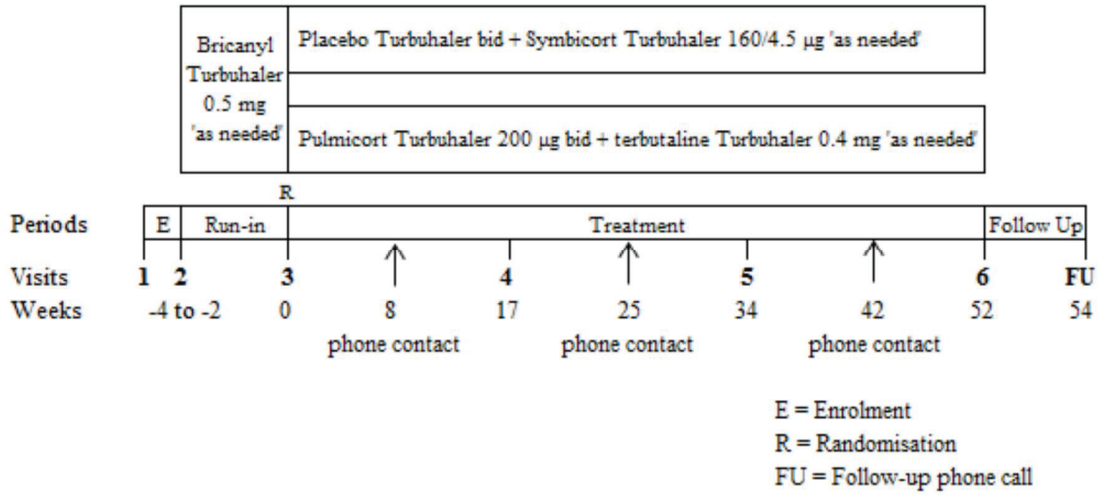


Table 1 Study assessments

	Enrolment	Run-in	Rando- misation	Treatment					6/ EoT^{a,b}	2 wks Follow-up
Visit	1	2	3	Phone call	4	Phone call	5	Phone call		Phone call
Week		-2 to -4	0	8	17	25	34	42	52	54
Visit window (days)	0-7 days before Visit 2	14-28 days before Visit 3		± 7	± 7	± 7	± 7	± 7	± 7	± 3
Written Informed consent	X									
Allocation of enrolment code	X									
Demography	X									
Inclusion/exclusion criteria	X	X	X							
Medical/surgical history	X									
Asthma history (including exacerbation history)	X									
Smoking history	X									
ACQ-5, AQLQ(S)		X	X		X		X		X	
Health Care resource utilisation questionnaire, EQ-5D-5L			X		X		X		X	
SAE/AEs ^c	X ^c	X ^c	X		X		X		X	X
Weight and height		X							X ^d	
Physical examination		X							X	

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	Enrolment	Run-in	Randomisation	Treatment						2 wks Follow-up
Visit	1	2	3	Phone call	4	Phone call	5	Phone call	6/ EoT ^{a,b}	Phone call
Week		-2 to -4	0	8	17	25	34	42	52	54
Visit window (days)	0-7 days before Visit 2	14-28 days before Visit 3		±7	±7	±7	±7	±7	±7	±3
Vital signs (pulse and blood pressure)		X							X	
Pregnancy test (if applicable)		X								
Adjustment of current asthma medication		X								
Patient training in how to use Turbuhaler (inhalation technique) and TUM		X								
Bricanyl for run-in (dispense/return)		d	r							
Randomisation			X							
Lung function (FEV ₁ , FVC pre- and post-Bricanyl administration)		X	X		X		X		X	
Reversibility test ^c		X	X ^c							
Collection of severe asthma				X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	
Concomitant medications		X	X		X		X		X	

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	Enrolment	Run-in	Rando- misation	Treatment					2 wks Follow-up	
Visit	1	2	3	Phone call	4	Phone call	5	Phone call	6/ EoT^{a,b}	Phone call
Week		-2 to -4	0	8	17	25	34	42	52	54
Visit window (days)	0-7 days before Visit 2	14-28 days before Visit 3		±7	±7	±7	±7	±7	±7	±3
Investigational product (dispense/return/ check)			d		d/r/c		d/r/c		r/c	

^a After discontinuation of IP (ie before Visit 6) patients will be followed up according to the original visit schedule including site visits and phone contacts. Only Severe asthma exacerbations, AEs and concomitant medications will be collected. If it is not possible for the patient to visit the study site, the visit(s) may be performed via phone. See CSP Section 4.4.

^b EoT is end of treatment visit.

^c Serious adverse events will be collected from time of signing Informed consent. Adverse events will be collected from Visit 2.

^d Height only for adolescents.

^e Reversibility test will be performed at Visit 2. The test can be repeated at Visit 3 in case the patients fail to meet inclusion criterion no. 6 at Visit 2. See CSP Section 3.1 for inclusion criteria.

^f Severe asthma exacerbations will be collected from Visit 3 through the entire study.

1.3 Number of patients

The study was originally powered to assess the primary objective of comparing Symbicort Turbuhaler ‘as needed’ versus Pulmicort Turbuhaler bid plus terbutaline Turbuhaler assuming that Symbicort Turbuhaler will be superior to Pulmicort Turbuhaler with regard to the annual severe asthma exacerbation rate. The change in the primary objective to non-inferiority did not lead to a sample size increase as Symbicort was assumed to be more efficacious (25%) than maintenance Pulmicort (in the same way that in the sample size calculation for the superiority test).

The severe exacerbation rate in the Pulmicort treatment group was estimated based on a retrospective Poisson regression on data from a subset of patients (in the Pulmicort group) from the START study ([Pauwels et al 2003](#)), as well as patients from the GOAL study treated with Fluticasone ([Bateman et al 2004](#)). The exacerbation rate in the START study was estimated to be 0.12 events per patient-year in the Pulmicort group. In the GOAL study, where patients were treated with Fluticasone, the exacerbation rate for the steroid naïve sub-population was also 0.12 events per patient-year, while for patients who had previously received low-dose steroid treatment, the exacerbation rate was 0.17 events per patient-year. Based on this information, the exacerbation rate for patients in the present study was estimated to be 0.16 events per patient-year. There was no evidence of over-dispersion in either study, so the shape parameter was assumed to be 0.

Calculations for estimating sample size were based on the following assumptions using a negative binomial model ([Keene et al 2007](#)):

- alpha 5%
- power 90%
- exacerbation rate of 0.16 in the Pulmicort treatment group
- 25% risk reduction in Symbicort vs Pulmicort
- no over-dispersion (shape parameter=0)

Based on these assumptions 3704 patients (1852 per arm) would be required. Accounting for a 10% drop-out gives a total sample size of 4114 patients (2057 per arm).

Sample size re-estimation: The relative lack of phase II data on Symbicort ‘as needed’ use in the target population means that there is a high degree of uncertainty about the assumed exacerbation rates and the dispersion parameter. To account for that uncertainty, the overall exacerbation rate will be monitored during the study. The maximum likelihood approach as proposed by [Friede and Schmidli, 2010](#) will be used to estimate the exacerbation rate and shape parameter. The reviews will be based on pooled, blinded data and will not use any treatment information. If the results of the blinded reviews indicate that the projected power falls to below 85%, the sample size may be increased. An allowance will be made for an increase in the sample size by a maximum of 50% i.e. up to a total of 6171 patients. Since this monitoring of the exacerbation rate will be performed in a blinded fashion, no adjustment for the type I error is needed.

Decision to change the primary objective from a superiority to non-inferiority hypothesis

In protocol amendment 4, the decision was made to change the primary objective to assess whether Symbicort Turbuhaler will be non-inferior to Pulmicort Turbuhaler with regard to the annual severe asthma exacerbation rate. Assuming a 25% exacerbation risk reduction in Symbicort vs Pulmicort, 0.14 overall exacerbation rate and no overdispersion, a total sample size of 4114 will provide at least 90% power to determine if Symbicort Turbuhaler is non-inferior to Pulmicort Turbuhaler with regard to the annual severe asthma exacerbation rate when the non-inferiority limit is set to 20% at the 5% (one-sided) significance level.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 All patients analysis set

This analysis set comprises all patients screened for the study and will be used for reporting of disposition and enrolment failures.

2.1.2 Full analysis set

All patients randomised and receiving any investigational product will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised treatment.

Twelve randomised patients from study site 5702 (Poland) will be excluded from the Full analysis set due to significant deviations. The deviations were mainly relating to unavailability, discrepancies and poor quality of source data which question the validity and integrity of the trial data generated from this site. Data listings for these 12 patients will be provided in Appendix 12.2 in the Clinical Study Report (CSR).

One randomised patient from study site 2612 (Germany) was randomised in error. Due to the subject age, local ethics committee decided data of this patient cannot be used for the analysis. Data listings for this 1 patient will be provided in Appendix 12.2 in the CSR.

The efficacy analysis will be based on the full analysis set (FAS) in line with the ICH E9 guideline.

Analysis of primary and secondary efficacy variables will be based on data recorded up to the discontinuation of investigational product (IP). Sensitivity analysis will be provided including the data post discontinuation of IP for the primary efficacy variable. Data for patients who withdraw consent to participate in the study will be included up to the date of their study discontinuation.

2.1.3 Safety analysis set

All patients receiving any investigational product will be included in the safety analysis population.

The following exclusions from the Safety Analysis Set will be made:

- 12 randomised patients from study site 5702 (Poland) will be excluded from the Safety analysis set due to significant deviations. The deviations were mainly relating to unavailability, discrepancies and poor quality of source data which question the validity and integrity of the trial data generated from this site. Data listings for these 12 patients will be provided in Appendix 12.2 in the CSR.
- 1 randomised patient from study site 2612 (Germany) was randomised in error. Due to the subject age, local ethics committee decided data of this patient cannot be used for the analysis. Data listings for this 1 patient will be provided in Appendix 12.2 in the CSR.

Patients will be classified according to the treatment they actually received. If a patient has a wrong kit id, then the treatment they actually received will be determined based on which treatment was used the most. All patients should be allocated to the safety analysis set prior to Database Lock (DBL), however the classification of treatment received, will not be determined until after unblinding, and will be documented. All safety summaries will be based on this analysis set.

2.2 Violations and deviations

Important protocol deviations will be listed and summarised by randomised treatment group and discussed in the CSR. None of the deviations will lead to any patients being excluded from any of the analysis sets described in Section 2.1. A per-protocol analysis excluding patients with important protocol deviation is not planned.

The following violations of inclusion criteria will be considered important protocol deviations when the study physician or principle investigator make a decision to discontinue the patient from the study due to one or more of these criteria. They will be identified using the CRIT and TERM Electronic Case Report Form (eCRF) modules.

- Diagnosis of asthma according to GINA criteria based on symptoms with a documented history of at least 6 months prior to Visit 1.
- Patients who are in need of GINA (2012) step 2 treatment:
 - uncontrolled on inhaled short-acting bronchodilator(s) 'as needed' (SABA and/or short acting anticholinergic agent) as judged by the investigator for the last 30 days before Visit 2, or
 - controlled on mono-maintenance therapy - with low stable dose Inhaled (gluco) corticosteroid (ICS) (≤ 400 µg budesonide per day or corresponding dose of other ICS) (see Appendix E for conversion) or LTRA - in addition to 'as needed' use of inhaled short-acting bronchodilator(s) (SABA and/or short acting anticholinergic agent), as judged by the investigator for the last 30 days prior to Visit 2

Based on lung function tests (see Section 5.1.2 of CSP) at Visit 2, patients pre-treated with

- an inhaled short acting bronchodilator only should have pre-bronchodilator FEV1 ≥ 60 % of predicted normal (PN) and post-bronchodilator FEV1 ≥ 80 % PN according to the European Respiratory Society (ERS) guidelines ([Quanjer et al 2012](#))
- low dose ICS or LTRA medication in addition to inhaled short-acting
- bronchodilator(s) should have pre-bronchodilator FEV1 ≥ 80 % PN according to the ERS guidelines
- Reversible airway obstruction according to a reversibility test (see Section 5.1.2.2 of CSP) performed at Visit 2 defined as an increase in FEV1 $\geq 12\%$ and ≥ 200 ml relative to baseline, after inhalation of 1 mg Bricanyl Turbuhaler.

The following violations of exclusion criteria will be considered important protocol deviations. They will be identified using the CRIT eCRF module only

- Medical history of life- threatening asthma including intubation and intensive care unit admission
- Any significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the results of the study, or the patient's ability to participate in the study

See the CSP Sections 3.1 and 3.2 for full definitions of the inclusion and exclusion criteria.

In addition to the programmatic determination of the deviations above, monitoring notes or summaries will be reviewed to determine any important post entry protocol deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified. The final classification will be made prior to database lock. There are two types of non-programmable important protocol deviation:

- Cases with severe noncompliance with study protocol potentially affecting primary endpoint as identified by study team physician during medical monitoring
- Wrong allocation of Kit I.D – Patient received IP from different treatment arm than assigned via Interactive Voice Response System (IVRS)

Due to treatment blinding, it will not be possible to identify if the wrong kit is different from the randomised treatment until after DBL.

All randomised patients who failed any inclusion/exclusion criteria will be listed along with details of the failed criteria. This information will also be summarised in terms of the number (%) of patient failing any of the inclusion/exclusion criteria and will be based on the FAS.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General considerations for outcome variables

3.1.1 Definition of baseline

Unless otherwise specified, the following general principles apply for determining the baseline for variables collected during scheduled visits.

Efficacy data collected at scheduled visits

The baseline value for variables collected during scheduled visits will be defined in two separate ways depending on how the data for that variable was collected.

Baseline for variables that included visit information will be defined as the last measured value prior to first dose of IP on Visit 3 only. I.e., no data from earlier visits will be used if Visit 3 data are missing. Baseline will be calculated using this method for the following variables:

- Lung function variables:
 - FEV₁ (L), pre- and post-bronchodilator*
 - FEV₁ % of predicted normal, pre- and post-bronchodilator*
 - Forced vital capacity (FVC) (L), pre- and post-bronchodilator*
- Exploratory variables:
 - EQ-5D-5L index score
 - EQ-5D-5L Visual analogue scale (VAS) score

*Note baseline post-bronchodilator values are calculated post-bricanyl, but before first dose of IP

Efficacy data with no visit information

Baseline for variables that did not include visit information will be defined as the last measured value prior to first dose of IP. Baseline will be calculated using this method for the following variables:

- Patient-reported outcomes:
 - ACQ-5 score
 - AQLQ(S) score

‘As needed’ medication

‘As needed’ medication at baseline is Bricanyl Turbuhaler 0.5 mg. Its baseline value is defined as average number of uses per day in the 10 days prior to randomisation during the run-in period. Each day for baseline will begin at 07:00 and end at 06:59:59 on the following day. It includes the last measurement taken on the morning of randomisation (prior to the first dose of maintenance medication, or 06:59:59, whichever is earlier).

‘As needed’-freedays

‘As needed’-free days at baseline is defined as number of days with no ‘as needed’ medication use (a day and a night) in the 10 days prior to randomisation during the run-in period. Percent ‘as needed’-free days at baseline will then be calculated as the number of ‘as needed’-free days at baseline divided by 10 multiplied by 100. Each day is calculated in the same way as the day calculation for ‘as needed’ medication in the previous section.

Safety data(vitalsigns and physical examination) and height

The baseline for vital signs (pulse rate and blood pressure), physical examination measurements and height is defined as the value recorded at Visit 2. If the Visit 2 record is missing, then baseline will be left as missing.

3.1.2 Definition of end of treatment

Patient-reported outcomes and exploratory variables

For patient reported outcomes end of treatment is defined as Visit 6, or the last visit for which the score of interest was calculated being the patient on study drug.

Safety data(vitalsigns and physical examination)

End of Treatment is the last scheduled visit prior to or on the day of last dose of IP.

3.1.3 Valid maintenance and ‘as needed’ medication turns

The use of maintenance and ‘as needed’ medication will be captured via the Turbuhaler Usage Monitor (TUM). This device is fitted to the Turbuhaler and records the timing of each turn of the inhaler.

A two-stage approach will be applied to exclude turns from the TUM which are considered impossible.

- (i) Turns taking place within ≤ 1 second of the previous turn will be excluded from analysis.
- (ii) The number of turns per day per inhaler will be limited to the number of available doses in each inhaler (120 as needed, 200 maintenance).

3.1.4 Timing of maintenance and ‘as needed’ medication and allocation to day/night period

‘As needed’ use (as recorded by the TUM) will be allocated to daytime and night-time periods in the following way:

- Start of the daytime period is defined as the time when the patient takes their morning maintenance dose (between 04:00-11:59:59). If the patient takes their morning maintenance dose before or after this time interval, or if there is no recorded morning maintenance dose the start of the daytime period will be set to the average of the recorded morning maintenance doses (between 04:00-11:59:59) across the trial for that patient. The end of the daytime period will be set one second prior to the start of the night-time period.
- Start of the night-time period is defined as the time when the patient takes their evening maintenance dose (between 18:00-23:59:59). If the patient takes their evening maintenance dose before or after this time interval, or if there is no recorded evening maintenance dose the start of the night-time period will be set to the average of the recorded evening maintenance doses (between 18:00-23:59:59) across the trial for that patient. The end of the night-time period will be set one second prior to the start of the daytime period. The final night-time period will occur on the day prior to last dose of IP, as no evening maintenance dose is expected on the final day.

For analyses where full days are assessed they are defined as a day followed by a night, with the start of each day defined by the start of the daytime period described above.

On the treatment start day, only those ‘as needed’ medications taken after the first maintenance medication will be considered to be in the randomised treatment period. Any ‘as needed’ medication taken prior to the first maintenance will be considered ‘run-in’ medication. If there is no maintenance medication on the treatment start day, then 12pm will be considered the end of run-in and start of the randomised treatment period. However, only those run-in ‘as needed’ medications recorded up to 06:59:59 will be included in baseline calculations.

On the treatment end day, only medications up to 18:59:59 will be included in the randomised treatment period.

For the purpose of calculating steroid load, maintenance medication will be assigned to each study day using the same windows as defined for the ‘as needed’ medication above.

For the purpose of study treatment compliance, and exposure, maintenance medication will be assigned to each study day if it occurs anytime from 4am on that study day until 3:59:59am on the following day (or 18:59:59 for the treatment end day). On treatment start day the start of the window will be 00:00:00 instead of 04:00:00.

A low proportion of data collected via the TUM were found to have a timestamp outside of the run-in period or the randomised treatment period. These records are excluded from all analysis.

3.1.5 Visit windowing

Details of the method for programming visit windowing is shown in [Appendix 4: Visit windowing](#).

3.1.6 Definition of completing treatment, completing study, randomised treatment period and study period

A patient will be considered as completing treatment if they have not discontinued IP prematurely according to the DOSDISC (dose discontinuation) module. If a patient does not have a record in DOSDISC, then a patient will be considered as completing treatment if they received treatment for ≥ 51 weeks. A patient will be considered as completing the study if they have not discontinued the study prematurely according to the TERM (Termination) module. The randomised treatment period is defined as the time from first dose of IP until the last dose of IP inclusive. The study period is the period from Visit 3 (Randomisation visit) up to Visit 6 (Week 52). A patients' follow-up time on randomised treatment is defined as the time from first dose of IP until the last dose of IP inclusive. A patients' follow-up time on study period is defined as the time from first dose of IP until the patient completes or pre-maturely withdraws from the study.

3.1.7 Definition of last dose of IP

The last dose of IP is defined as the date of discontinuation of IP if available, otherwise end date of dosing if available, otherwise date of termination if available.

3.2 Primary variable

The primary efficacy variable is the annual severe asthma exacerbation rate.

The definition of the event “a severe asthma exacerbation” and method for deriving the primary variable is given in Section [3.4.1](#) below.

3.3 Demography and patient characteristics

3.3.1 Demography, weight and height

The following demographic data will be collected at enrolment (Visit 1):

- Date of birth
- Gender
- Race/ethnicity population

Race and ethnicity information will be collected as per AstraZeneca standards using the standard race and ethnicity categories stipulated in FDA guidance. However, for the purposes of calculating multi-ethnic predicted normal values of FEV₁ ([Quanjer et al 2012](#)), a different categorisation of ethnicity is required. This variable is collected as “ethnic population” in the subject characteristics (SC) module of the eCRF. See Section [3.4.6](#) for further details on the calculation of predicted normal FEV₁.

Weight in kilogram and height in cm will be measured at Visit 2. For adolescents (i.e. patients aged less than 18 years at the date of informed consent), height will additionally be measured at Visit 6. Body mass index [weight in kg / (height in m)²] will be categorised as (<25, ≥25 and <30 and ≥ 30).

Age at date of informed consent (in terms of whole years lived) will be derived using date of birth and date of Visit 1. It will be categorised (≥12 and <18, ≥18 and <50, ≥50 and <65, ≥65 and <85 and ≥ 85 years of age).

Region will be defined as follows:

- *Latin America*: Argentina, Brazil, Chile, Colombia, Mexico, Peru
- *EU*: Bulgaria, Czech Republic, France, Germany, Hungary, Romania, Slovakia, Spain, Sweden
- *East Asia*: Philippines, South Korea, Thailand, Vietnam
- *Rest of World*: Australia, New Zealand, Russia, Saudi Arabia, South Africa, Ukraine

For the purpose of calculating predicted normal lung function variables (FEV₁, and FVC), age at the day the test is conducted will be calculated to the nearest 0.01 years. Height for adults will be assumed to be constant throughout the course of the study. Further details on the use of demographic variables for calculating predicted normal FEV₁ is given in Section 3.4.6.

3.3.2 Medical, asthma and smoking history

Medical (incl. surgical), asthma (incl. exacerbations) and smoking history (smoking status and the number of pack years consumption) are recorded during the enrolment visit (Visit 1).

3.4 Efficacy variables

3.4.1 Severe asthma exacerbation

3.4.1.1 Definition of severe asthma exacerbation

A *severe exacerbation* is defined as a deterioration of asthma requiring any of the following:

- use of *systemic* glucocorticosteroids (GCS) for at least 3 days¹,
- inpatient hospitalization, or
- emergency room visit² due to asthma that required systemic steroids³.

¹ An injection of depot corticosteroids due to asthma worsening is considered equivalent to at least 3 days of systemic corticosteroids. If duration of GCS is missing, a conservative approach is taken and duration is assumed ≥ 3 days.

² Emergency room visit or other urgent unscheduled health care visit

³ Systemic steroids used for any length of time.

For severe exacerbations, the start date is defined as the first day of hospitalisation/emergency room treatment or the first day of systemic (i.e. not inhaled) GCS treatment. The end date is defined as the last day of hospitalisation/emergency room treatment or the last day of systemic GCS treatment (according to prescription). If the same asthma exacerbation includes both hospitalisation/emergency room treatment and systemic GCS treatment, the start and end dates are the first and last day that either of the criteria was fulfilled. No date imputation is done for severe exacerbations with missing end dates.

Additional hospitalisations/emergency room treatments and systemic GCS treatments occurring during a severe asthma exacerbation should not be regarded as a new exacerbation.

For a severe asthma exacerbation to be counted as a separate event, it must be preceded by at least seven days in which no criteria for severe exacerbations are fulfilled.

3.4.1.2 Number of severe asthma exacerbations, and annual severe exacerbation rate

The total number of severe asthma exacerbations during the 52-week double-blind randomised treatment period will be calculated for each patient, following the method set out in Section 3.4.1.1.

In order to account for varying lengths of follow-up time (due to early study drug discontinuation, early study withdrawal, patient lost to follow-up, or minor differences of the timing of Visit 6), the *annual severe exacerbation rate* will be presented for the purposes of summary statistics. This will be calculated on a study level as follows:

$$\text{Study level: Annual severe exacerbation rate} = \frac{\sum \text{Number of severe exacerbations} * 365.25}{\sum (\text{Date of last dose of IP} - \text{date of first dose of IP} + 1)}$$

For patients who discontinue randomised study drug pre-maturely but remain in the study, severe asthma exacerbation data will continue to be collected according to the original visit schedule for sensitivity analysis described in Section 4.2.8.3. Number of severe asthma exacerbations will also include those data collected after discontinuation of randomised study drug, and up to last visit (Visit 6). The *annual severe exacerbation rate* for the purpose of sensitivity analysis will be calculated on a study level as follows:

$$\text{Study level: Annual severe exacerbation rate (SA)} = \frac{\sum \text{Number of exacerbations captured during study period} * 365.25}{\sum (\text{Date of latest follow-up prior to or on Visit 6} - \text{date of first dose of IP} + 1)}$$

3.4.1.3 Time to first severe asthma exacerbation

The start and end dates of each severe exacerbation will be recorded in the eCRF at the site visits. From the start date and the date of first dose of IP, the time to first severe asthma exacerbation will be calculated as below:

Time to first severe asthma exacerbation = Start date of first severe asthma exacerbation – Date of first dose of IP + 1

Patients not having any severe asthma exacerbation will be considered censored at their latest follow-up date whilst in the randomised treatment period. The latest follow-up date is defined as the last dose of IP as defined in Section 3.1.7.

Time to censoring in days is then calculated as follows:

Time to censoring = Date of latest follow-up date on IP – Date of first dose of IP + 1

3.4.2 Medication-based outcomes

3.4.2.1 ‘As needed’ medication use

‘As needed’ use during the randomised treatment period will be calculated as the cumulative doses of ‘as needed’ medication divided by the number of days in the randomised treatment period (*Date last dose of IP – date of first dose of IP + 1*).

For Symbicort treatment arm ‘as needed’ will be Symbicort, while for the Pulmicort treatment arm ‘as needed’ will be terbutaline.

Measurement of ‘as needed’ use is defined as the number of turns of the inhaler captured via the TUM device. Change from baseline will be calculated for each patient, where baseline is defined as in Section 3.1.1. As TUM device is capturing the number of turns by day and by night, ‘as needed’ medication use will be defined by day, by night and by total as defined in Section 3.1.4.

For total and night mean number of ‘as needed’ medication uses, the final day of treatment will not be included as part of the randomised treatment period. This is due to the patients returning their TUM prior to the final evening.

3.4.2.2 Daily end-points

‘As needed’-freedays

An ‘as needed’-free day is defined as a day and night with no use of ‘as needed’ medication. Percent ‘as needed’-free days will then be calculated as the number of days during the randomised treatment period with no record in the TUM device of ‘as needed’ medication divided by the number of days in the randomised treatment period multiplied by 100. Change from baseline will then be calculated for each patient, where baseline is defined as in Section 3.1.1.

ICS controller use days

A controller use day is defined as a day and night with any use of controller medication.

Controller use during the randomised treatment period will be calculated as the cumulative days when any controller medication (containing ICS) was taken divided by the number of days in the randomised treatment period (date of last dose of IP – date of first dose of IP + 1).

For the Symbicort treatment arm, the controller will be the ‘as needed’ medication. For the Pulmicort treatment arm, the controller will be the maintenance medication. Plus, any additional prescribed inhaled corticosteroid for asthma exacerbations which is applicable for all treatment arms. Controller use will be derived using data collected from the TUM device, additional prescribed inhaled corticosteroids are collected via the MED and EXACASI modules of the eCRF and defined in Appendix 2.

The denominator for percentage of ‘as needed’ free-days and controller use days will be 10 days for the baseline period (‘as needed’-free days only), and (date of last dose of IP – date of first dose of IP + 1) for the randomised treatment period.

3.4.3 Total inhaled steroid load

Data on additional inhaled and systemic steroids prescribed for exacerbations will be collected via the *EXACASI* eCRF module. Additional ICS and systemic GCS prescribed on the day of IP discontinuation for an asthma exacerbation will be considered as during the randomised treatment period, otherwise they will be considered as during the follow-up period (See Appendix 2).

Total inhaled steroid load (total ICS dose) during the randomised treatment period will be calculated for each patient as the sum of the cumulative doses of maintenance ICS (budesonide), ‘as needed’ ICS as part of Symbicort (budesonide), and additional prescribed inhaled corticosteroids of any type.

For calculation purposes, the dose for ‘as needed’ ICS part of the Symbicort arm will be the delivered dose, 160µg. The maintenance ICS part of the Pulmicort arm will be converted from the metered dose, 200µg to 160µg, the delivered dose. For additional ICS, the dose, as recorded by the investigators in the eCRF will be used.

Doses which are not in µg should be converted to µg before being summed. For additional prescribed inhaled corticosteroids, 100% compliance will be assumed. Data on IP usage will be recorded via the TUM, while additional prescribed inhaled corticosteroids will be collected via the appropriate CRF module, and can be identified as per the table in Appendix 2.

To account for differences in the length of follow-up, a time-standardised variable, *mean daily ICS dose*, will be estimated. This will be calculated separately for each patient, and then averaged over all patients:

Total ICS: Mean daily ICS dose = Total ICS dose / (Date of last dose of IP – Date of first dose of IP + 1)

The mean daily ICS dose will also be calculated separately for IP [maintenance ICS (budesonide), ‘as needed’ ICS as part of Symbicort (budesonide)] and additionally prescribed ICS. Also, additionally prescribed ICS will be separated by individual ICS medications.

IP: Mean daily ICS dose = Total ICS dose (IP only) / (Date of last dose of IP – Date of first dose of IP + 1)

Additional ICS: Mean daily ICS dose = Total ICS dose (Additional only) / (Date of last dose of IP – Date of first dose of IP + 1)

If there is no available end date for additional ICS, then it will be assumed that it continues until IP discontinuation.

3.4.4 Number of days with systemic GCS treatment due to asthma

The number of days with systemic GCS due to asthma will be recorded via the eCRF MED module (identified as per the table in Appendix 2) at each visit. The total number of days recorded during the randomised treatment period will then be calculated for each patient.

3.4.5 Time to study specific asthma-related discontinuation

The following criteria should lead to discontinuation from the IP due to asthma related events:

- A severe asthma exacerbation with duration for more than 3 weeks
- Three severe asthma exacerbations during 6 months

For patients who experience one of these events, time to discontinuation of IP due to any of the specified asthma related events will be calculated as:

Time to discontinuation of IP due to any asthma-related event = Date of study drug termination due to any asthma-related event – Date of first dose of IP+ 1

Time to censoring will be defined as for censoring for asthma exacerbations (see Section 3.4.1.3), with the exception that only patients who discontinued the study for any reason other than one of the pre-defined asthma-related events will be censored as of their discontinuation date.

3.4.6 Lung function variables

The following lung function measurements will be calculated at Visits 2, 3 (baseline), 4, 5 and 6, at two time-points per visit (pre- and post-bronchodilator):

- FEV₁ (L)
- FEV₁ % of predicted normal (PN)
- FVC (L)

In addition, a treatment average will be calculated within subject as the average of Visits 4 to 6 (one value per visit). Change from baseline for each of these three variables, for both time-points will also be calculated for Visits 4, 5, 6 and treatment average. Please refer to Section 3.1.1 for the baseline definition.

FEV₁ predicted normal will be derived using the patient's age (to the nearest 0.01 years, at the time of the visit), height (for adults, measured at screening; for adolescents, interpolated between measurements taken at Visits 2 and 6) and ethnic population, following the Global Lung Initiative

(GLI) 2012 lung function regression equations (Quanjer et al 2012). Full details of how this method is applied can be found in [Appendix 1: Method for calculating predicted normal FEV₁](#).

Percentage of predicted normal FEV₁ is then calculated as follows:

$$FEV_1 (\% \text{ of PN}) = 100 \times (FEV_1 (\text{actual}) / FEV_1 (\text{predicted}))$$

3.4.7 Patient reported outcomes

3.4.7.1 Asthma Control Questionnaire – 5-item Version (ACQ-5)

The 5-item version of the ACQ questionnaire contains five questions on patients' symptoms, which are assessed on a 7-point scale from 0 (representing good control) to 6 (representing poor control). The ACQ score is the mean score of all questions for which responses are provided. A minimum of 4 out of 5 questions must be answered for a valid ACQ-5 score.

The ACQ is conducted at Visits 2, 3, 4, 5 and 6, with the score evaluated at each visit. Change from baseline for Visits 4, 5 and 6 (individual visits, end of treatment and average across Visits 4 to 6) will also be calculated (baseline calculated as described in Section 3.1.1).

End of treatment is defined in Section 3.1.2. The following categorical outcome variables will be calculated based on ACQ-5 score at the end of treatment:

- Asthma control at end of study: ACQ-5 score at end of treatment $< 0.75, \geq 0.75$
- Patient improved: Δ_{BL} (ACQ-5 score) at end of treatment ≤ -0.5
- Patient unchanged: Δ_{BL} (ACQ-5 score) at end of treatment $\in (-0.5, 0.5)$
- Patient worsened: Δ_{BL} (ACQ-5 score) at end of treatment ≥ 0.5 where $\Delta_{BL}(x)$ denotes "Change from baseline in x ".

Note: Patient improved/unchanged/worsened responses are based on a minimal important difference (MID) of 0.5.

If more than one ACQ-5 is completed on any day, the questionnaire with the worst score (highest mean value) will be used in the analysis. This applies to both baseline and post-baseline assessments.

3.4.7.2 Asthma Quality of Life Questionnaire – Standardised version (AQLQ(S))

The AQLQ(S) includes 32 questions relating to 4 distinct domains:

- activity limitation (11 questions; minimum 7 questions required for a valid score)
- symptoms (12 questions; minimum 8)
- emotional function (5 questions; minimum 3)

- exposure to environmental stimuli (4 questions; minimum 3)

Each question is answered on a 7-point scale ranging from 1 to 7 with lower values representing more severe impairment.

For each of the four domains, a domain score is calculated as the mean score of all its constituent items (this is defined as missing if the minimum number of questions required for a valid score is not met). An overall score across the whole questionnaire is calculated as the mean score of all 32 items. In case of any missing answers, the overall score is calculated as a weighted mean of the domain scores, with the nominal fraction of items in each domain as weights. If one or more domains are missing, the overall score is also missing. (Note: when there are no missing answers, this method is equivalent to the average response of all 32 questions taken individually.)

The four domain scores and an overall score will be calculated for Visits 2, 3, 4, 5 and 6. Change from baseline for all four domain scores and the overall score will be calculated for Visits 4, 5 and 6 (individual visits, end of treatment and average across Visits 4 to 6) will also be calculated (baseline calculated as described in Section 3.1.1).

End of treatment is defined in Section 3.1.2. The following categorical outcome variable will be calculated based on *overall* AQLQ(S) score at the end of treatment:

- Patient improved: $\Delta_{BL}(\text{AQLQ(S) score}) \text{ at end of treatment} \geq 0.5$
- Patient unchanged: $\Delta_{BL}(\text{AQLQ(S) score}) \text{ at end of treatment} \in (-0.5, 0.5)$
- Patient worsened: $\Delta_{BL}(\text{AQLQ(S) score}) \text{ at end of treatment} \leq -0.5$ where $\Delta_{BL}(x)$ denotes “Change from baseline in x ”.

Note: Patient improved/unchanged/worsened responses are based on a MID of 0.5.

If more than one AQLQ(S) is completed on any day, the questionnaire with the worst overall score (lowest mean value) will be used for the analysis. This applies to both baseline and post-baseline assessments.

3.5 Safety variables

3.5.1 Vital signs

The following vital signs measurements will be conducted at Visits 2 and 6 (or discontinuation of IP):

- Pulse rate
- Systolic blood pressure
- Diastolic blood pressure

Vital signs measurements will continue to be collected in patients who discontinue IP prematurely. Change from baseline for all three variables will be defined as the difference between measurements at Visit 6 (or discontinuation of IP) and Visit 2 (as per Section 3.1.1 above).

3.5.2 Physical examination

The following physical examination assessments will be made at Visits 2 and 6 (or discontinuation of IP):

- General appearance
- Respiratory
- Cardiovascular
- Abdomen
- Head and neck (including head, ears, eyes, nose and throat)

3.5.3 Adverse events (including Serious Adverse Events)

3.5.3.1 Collection of AEs and SAEs

Adverse Events (AEs) will be collected from Visit 2 throughout the treatment period and including the follow-up period until the last telephone follow-up, or the last contact.

Serious Adverse Events (SAEs) will be recorded from the time of informed consent (Visit 1).

The following assessments will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity (mild/moderate/severe)
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE

- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE

3.5.3.2 Definition of adverse event leading to discontinuation of investigational product (DAE)

Adverse events where “Action taken with regard to investigational product” is answered “discontinued” will be defined as DAEs and reported separately (in addition to being reported as general AEs).

3.5.3.3 AEs representing potential β 2 agonist effects and AEs representing potential ICS effects

Summary tables of AEs representing potential β 2 agonist effects and AEs representing potential ICS effects will be produced (See [Appendix 3: Potential class effects \$\beta\$ 2-agonists and Potential ICS effects](#)).

3.5.3.4 Other significant adverse events (OAEs)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert’s judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of vital signs data will be performed for identification of OAEs.

OAEs will be reported in a separate table (in addition to being reported as general AEs).

3.5.3.5 Adverse events data handling

Adverse events will be reported as occurring during the run-in period if the start date is on or after the first date of run-in medication, and prior to the first dose of randomised medication.

Adverse events will be considered as occurring during the randomised period if the onset date is on or after the date of first dose of randomised study medication and onset is not later than one day after the last day of randomised treatment.

Adverse events that start during the run-in period but continue and become serious adverse events during the randomised period will be reported in both run-in and also in the randomised treatment period.

Adverse events will be considered as occurring during the follow-up period if the onset date is later than one day after the last day of randomised treatment.

Adverse events will be considered as occurring during the follow-up period if the onset date is later than one day after the last day of randomised treatment.

If an AE has a missing onset date, then, unless the stop date of the AE indicates otherwise, this will be considered as occurring during the randomised treatment period. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered as occurring during the randomised treatment period.

3.6 Other variables

3.6.1 Concomitant medications

Concomitant inhaled and systemic asthma treatment as prescribed in response to severe exacerbations will be recorded in the *EXACASI* eCRF module with medication specified in the MED module.

Other concomitant medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Additional ICS and systemic GCS prescribed on the day of IP discontinuation for an asthma exacerbation will be considered as during the randomised treatment period, otherwise they will be considered as during the follow-up period (See Appendix 2). All other concomitant medication prescribed on the day of IP discontinuation will be counted as during the randomised treatment period unless the reason is 'disease under study' where it will be considered as follow-up.

3.6.2 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patients that are incorrectly enrolled and/or randomised to study
- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the study protocol

- Safety reason as judged by the investigator and/or AstraZeneca
- Pregnancy
- Development of any of the following study specific criteria for discontinuation:
 - A severe asthma exacerbation with duration of more than 3 weeks
 - Three severe asthma exacerbations within a period of 6 months

In these cases, the reason for withdrawal from the study will be “Discontinuation of investigational product” and the reason for discontinuation will also be recorded.

Time to discontinuation from IP due to any of the specified reasons will be calculated as:

Time to discontinuation of IP = Date of study drug termination – Date of first dose of IP + 1

Time to censoring will be calculated using same methodology as described for asthma exacerbations (see Section 3.4.1.3).

3.6.3 Compliance of study maintenance medication

Summary statistics about maintenance medication compliance will be produced. For expected maintenance inhalations, only one maintenance dose is expected on the final day of treatment.

Compliance for maintenance medication (%) will be calculated for each patient as:

*(Total actual maintenance inhalations/Total expected maintenance inhalations)*100.*

*Total expected maintenance inhalations = number of days in randomised treatment period * 2 - 1*

Other compliance metrics includes the proportion of study days where patients used no doses, 1-2 doses only, 2 doses only, and more than 2 doses.

For the purpose of graphical representation, the proportion of study days where patients used ≥ 1 inhalation will also be calculated per week as follows:

- Derive the percentage per day as number of patients who took at least 1 inhalation divided by the number of patients still in the randomised treatment period on the respective study day.
- For each week take a mean of the percentages for the 7 days of the week.

4. ANALYSIS METHODS

4.1 General principles

All tests will be 2-sided and at 5% level of significance unless otherwise stated. No adjustment will be made for multiplicity, except for the primary variable annual severe exacerbation rate, which is described in Section 4.2.5.1.

For all statistical analyses, missing at random (MAR) will be assumed. Missing not at random (MNAR) mechanism will be explored as a sensitivity analysis of the primary variable annual severe exacerbation rate, further described in Section 4.2.8.3.

In addition to the analyses described below, all variables will be summarised descriptively, as appropriate.

For efficacy analysis, the following general principles guide the statistical hypotheses to be tested:

- The two treatment groups in the study (with short names defined for clarity) are as follows:
 - Symbicort Turbuhaler 160/4.5µg ‘as needed’ with no maintenance treatment (Symbicort ‘as needed’)
 - Pulmicort Turbuhaler 200µg twice daily ‘maintenance’ plus terbutaline Turbuhaler 0.4mg ‘as needed’ (Pulmicort bid)
- For the purpose of this statistical analysis plan (SAP), the treatment that a patient has been randomised to for the duration of the study will be referred to simply as ‘treatment’; treatment prescribed to a patient prior to the study will be referred to as ‘pre-study treatment’.

The two pre-study treatment groups are defined as follows:

- Uncontrolled on an inhaled short-acting BD 'as needed' (SABA and/or short-acting anticholinergic agent)
- Controlled on ICS or LTRA: Controlled on mono-maintenance therapy with either a low dose ICS or a LTRA in addition to 'as needed' use of inhaled short-acting BD (SABA and/or short-acting anticholinergic agent).

Unless otherwise stated all efficacy and safety analyses will be conducted using the “randomised treatment period” which begins at date of first dose of investigational product (maintenance or ‘as needed’ study medication). It ends at the end date of dosing if available, otherwise date of termination if available, otherwise last visit date

Any AE starting or worsening during the randomised treatment period up to 1 day after IP discontinuation is considered treatment emergent..

4.2 Analysis methods

4.2.1 Patient disposition

Patient disposition will be summarised using the All Patients analysis set. The number of patients who were enrolled, run-in and not run-in will be summarised. The number and percentage of patients within each treatment group will be presented by the following categories; randomised, not randomised (and reasons), randomised who received study treatment, randomised who did not receive study treatment (and reasons), completed randomised treatment, pre-maturely discontinued randomised treatment (and reasons), and completed the study and patients withdrawn from study (and reasons).

A separate table will present the number and percentage of patients randomised to each treatment group by region and country. This table will be based on the FAS.

4.2.2 Demography data and patient characteristics

Age, gender, race, ethnic group and region will be summarised by treatment group and by treatment and pre-treatment group for the full analysis set. Baseline characteristics will be summarised by treatment for the full analysis set. These include previous disease-related treatments, medical and surgical histories. Weight, height, body mass index, smoking status, and ACQ and AQLQ questionnaires will be summarised by treatment, and by treatment and pre-study treatment group. FEV₁ (pre- and post-bronchodilator) and reversibility (ml and %) will be summarised during run-in and at baseline by treatment, and by treatment and pre-study treatment. Asthma duration (defined by Time in years since asthma diagnosis, and Time in years since asthma symptoms started), a binary variable capturing if the most recent severe exacerbation was in last 12 months (Yes/No), and the number of severe exacerbations in the previous 12 months will be summarised by randomised treatment group, for all patients and by pre-study treatment subgroup at the enrolment visit.

FEV₁ % predicted normal (pre-bronchodilator and post-bronchodilator) as assessed at study entry and baseline will also be categorised into the following four categories for pre-bronchodilator measurements: < 60%, ≥60% to < 80% , ≥80% to <100%, ≥100%, and for post-bronchodilator measurements the categories are: <80%, ≥80% to <100%, ≥100%. The number of patients and percentage of patients falling into each of these categories and treatment group will be presented both in total, and by each pre-treatment subgroup.

Medical and surgical histories will be summarised by MedDRA preferred term (PT) within MedDRA system organ class (SOC).

4.2.3 Concomitant medication

The number and percentage of patients who take allowed concomitant medications, and those who take disallowed concomitant medications during the study, will be presented by treatment group. Concomitant medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). The summary tables will present data by generic term within (Anatomical Therapeutic Chemical) ATC code for the full analysis set.

4.2.4 Exposure to study treatment

Exposure to study treatment during randomised treatment period will be summarised for the Safety Population. It will be calculated as the date of last dose – date of first dose + 1. Descriptive statistics will be presented by treatment group, and by treatment group and pre-study treatment group. Cumulative exposure will also be presented by treatment group, and by treatment group and pre-study treatment group and also summarised by the following categories: ≥ 1 day, >4 weeks, >8 weeks, >16 weeks, >24 weeks, >32 weeks, >40 weeks, >48 weeks and >52 weeks of study treatment exposure.

4.2.5 Primary efficacy analysis

4.2.5.1 Annual severe asthma exacerbation rate

The primary variable, annual severe asthma exacerbation rate, will be analysed by a negative binomial regression model. The response variable in the model will be the number of severe asthma exacerbations over the randomised treatment period. The model will include randomised treatment, pre-study treatment group and region as factors. The logarithm of the follow-up time will be used as an offset variable to adjust for patients having different exposure time of randomised study treatment. Where the follow-up time is defined as the time the patient was on randomised study drug.

The evaluation of the treatment effect will take place in a step-wise order:

Step 1: The Negative binomial regression model will be fitted to the FAS, including patient data up to study drug discontinuation, but for this particular analysis excluding patient data from France (9 randomised patients in total). From this model, the annual severe asthma exacerbation rates will be estimated using least square means, and the treatment effect will be expressed as the rate ratio along with its corresponding 1-sided 95% confidence interval (CI). Output from this analysis will be used to evaluate the non-inferiority hypothesis as stated below:

Symbicort vs Pulmicort (non-inferiority, primary objective)

Formally, the null and alternative hypothesis are:

$$H_0: \text{rate-ratio (Symbicort vs Pulmicort)} \geq 1.2$$

$$H_1: \text{rate-ratio (Symbicort vs Pulmicort)} < 1.2$$

If the upper 1-sided 95% confidence limit of the rate-ratio is < 1.2 then non-inferiority can be declared. If the criteria for the alternative hypothesis is met, then superiority of Symbicort vs Pulmicort in terms of annual severe asthma exacerbation will be assessed (Step 2 below).

Step 2: The same Negative binomial regression model will be fitted to the FAS, including *all* patient data up to study drug discontinuation. From this model, the annual severe asthma exacerbation rates will be estimated using least square means, and the treatment effect will be expressed as the rate ratio along with its corresponding 2-sided 95% CI and p-value. Output from this analysis will be used to evaluate the superiority hypothesis as stated below:

Formally, the null and alternative hypothesis for superiority testing is:

H_0 : rate-ratio (Symbicort vs Pulmicort) = 1

H_1 : rate-ratio (Symbicort vs Pulmicort) \neq 1

The 95% 2-sided CI will be evaluated for the superiority hypothesis.

The Negative Binomial regression model will be coded using the PROC GENMOD procedure in SAS®, using the following code as a guide:

```
proc genmod data=indata;  
  class trtcd pst region;  
  model nexac = trtcd pst region / dist=negbin offset=logfup;  
run;
```

The rate ratio estimates together with the corresponding 1-sided and two-sided 95% CI will be shown in a Forest plot.

4.2.6 Secondary efficacy analyses

4.2.6.1 Severe asthma exacerbation variables

Time to first severe asthma exacerbation will be analysed by Cox proportional hazards model with randomised treatment, pre-study treatment group and region as factors. The hazard ratio and its corresponding 95% CI will be estimated from the model. A Kaplan-Meier plot for time to first severe exacerbation will be generated.

The Cox proportional hazards model will be coded using PROC PHREG in SAS®, using the following code as a guide:

```
proc phreg data=indata;  
  class trtcd pst region;  
  model texac*censor(0) = trtcd pst region;  
run;
```

All severe exacerbations, severe exacerbations requiring hospitalisation, severe exacerbations requiring systemic steroid use for at least 3 days, and severe exacerbations requiring emergency room visit and systemic steroids (total number, patients with at least one and annual rate) will be summarised using descriptive statistics and will be presented by treatment group. Further, number of severe exacerbations per patient (continuous and categorical), total days of exacerbation, average duration of exacerbation in days for the all severe exacerbations and the three components described above. Additionally, a time-event plot displaying each severe exacerbation by patient will be generated.

A table presenting the total number of severe exacerbations, and the total number and percentage of these events that were preceded by a worsening of asthma symptoms within 24 hours, including type of symptom, will be presented by each randomised treatment group. A graphical display

showing the average of ‘as needed’ inhalations by day from 14 days before to 14 days after the onset of a severe asthma exacerbation by treatment will be produced.

4.2.6.2 Discontinuation of IP due to study specific asthma related events

Time to study specific discontinuation of IP due to asthma related events will be analysed by Cox proportional hazards model with treatment, pre-study treatment group and region as factors. The hazard ratio and its corresponding 95% CI will be estimated from the model (as with time to first severe asthma exacerbations in Section 3.4.1.3).

Summary statistics alone will be presented if the number of study-specific asthma related discontinuations is considered to be too small to enable a meaningful statistical analysis.

In addition, the number of patients and the percentage of patients meeting a study specific asthma related discontinuation criterion, will be presented by randomised treatment group for the FAS. The table will include both the total and also each of the two discontinuation criteria: Severe asthma exacerbation with duration for more than 3 weeks, and Three severe asthma exacerbations during 6 months.

4.2.6.3 Discontinuation of IP and study withdrawal

Kaplan-Meier plots will be produced showing Time to discontinuation of IP and Time to study withdrawal in unit weeks by treatment group for the FAS. Time to discontinuation of IP will be the time from first dose of IP to time of IP discontinuation or completion (whatever occurs first). Time to study withdrawal will be the time from first dose of IP to time of study withdrawal or completion (whatever occurs first).

4.2.6.4 Steroid load

The mean daily ICS (IP only, additional ICS and total, in μg) and the number of days with systemic GCS due to asthma will be presented descriptively by randomised treatment. A line graph will examine the change in mean daily inhaled steroid load over the randomised treatment period, by study week. In addition, a box and whisker plot presenting the mean daily ICS dose during the randomised treatment period, by each randomised treatment group will be produced. Within each treatment group there will be three different boxes presented: first box representing the total ICS, second box presenting the IP only ICS and the third box presenting additional ICS use.

4.2.6.5 Lung function measurements

The treatment effect for change from baseline in FEV₁ (measured in litres) will be estimated using a mixed model repeated measures (MMRM) analysis. Pre- and post-bronchodilator FEV₁ will be analysed in separate models, using the same modelling method.

For each model (pre- and post-bronchodilator) measurements of the outcome variable will be taken at Visits 4, 5, and 6. Terms for randomised treatment, pre-study treatment, region, visit and (randomised treatment*visit) will be included as fixed effects. Patient will be included as a random effect. Baseline FEV₁ will be included as a continuous covariate. Visit will be fitted as an unordered categorical variable, and the variance-covariance matrix will be assumed to be

unstructured. The model will be coded using the PROC MIXED procedure in SAS® using the following code as a guide:

```
proc mixed data=indata;  
  class trtcd pst region visit;  
  model chg = trtcd pst region visit trtcd*visit base/ddfm=kr;  
  repeated visit / subject=usubjid type=un;  
run;
```

If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead (replacing `type=un` with `type=cs` in the above code).

Kenward-Roger denominator degrees of freedom will be used ([Kenward and Roger 1997](#)).

This model will be used to give an overall assessment of the treatment effect as well as 95% CIs. Separate treatment effects per visit will be presented. Graphical plots of the treatment effect for pre- and post- bronchodilator FEV₁ (Least Squares Means and 95% CI) over time will also be presented.

Summary statistics will be presented by treatment for pre- and post-bronchodilator FEV₁ (L), FEV₁ (% of predicted normal) and FVC (L) (including change from baseline in those variables) across all the visits in the trial. Graphical plots of the FEV₁ variables above over time will also be presented using model estimates.

4.2.6.6 Patient reported outcomes

ACQ-5 and AQLQ will be analysed in the same way as FEV₁ using MMRM analysis using the corresponding baseline values. Figures showing the treatment effect for ACQ-5 and AQLQ overall scores (LSMeans and 95% CI) over time will also be presented.

Responder variables based on a clinical improvement in ACQ-5 and AQLQ(S) of MID at end of treatment compared to baseline and the responder variable ACQ-5 < 0.75 at the end of treatment will be analysed using logistic regression models. For each outcome variable, the model will include randomised treatment, pre-study treatment and region as factors, and baseline ACQ-5 or AQLQ(S) score (whichever matches the outcome variable in question) as a continuous covariate. From the logistic regression model treatment effects will be estimated by odds-ratio and its corresponding 95% CI.

The model will be coded using the PROC LOGISTIC procedure in SAS® using the following code as a guide:


```
proc logistic data=indata;  
  class trtcd pst region;  
  model resp = trtcd pst region base;  
run;
```

In addition, the proportion of patients who had a clinical worsening or no clinically meaningful difference in ACQ-5 and AQLQ(S) based on MID at end of treatment compared to baseline will be reported.

Translation issues were identified in some versions of the ACQ-5/AQLQ questionnaires in some countries. Any patient who completed an ACQ-5 questionnaire with a translation issue will be excluded from all ACQ-5 analysis. Any patient who completed an AQLQ questionnaire with a translation issue will be excluded from all AQLQ analysis

Descriptive statistics for absolute and change from baseline values in ACQ-5 and AQLQ (total and domain scores) will be presented by treatment across visits, treatment average and end of treatment.

Graphical plots of change from baseline ACQ and AQLQ over time will also be presented using model estimates.

4.2.6.7 ‘As needed’ use, Percent ‘as needed’ free days, and Percent controller use days

Summary statistics about ‘as needed’ medication use and change from baseline in ‘as needed’ medication use will be produced for day, night and total respectively by treatment. The average number of ‘as needed’ inhalations and days with no inhalations, with 1 to 2, with 3 to 5, with 6 to 8, with 9 to 12 and more than 12 inhalations will be analysed using descriptive statistics.

Summary statistics about high use of ‘as needed’ medication (>8 and >12 inhalations on one day) will also be produced. A line graph will examine the mean ‘as needed’ medication use over the randomised treatment period for daytime, nighttime and total.

Change from baseline in ‘as needed’ medication use will be analysed using analysis of covariance (ANCOVA) models. Day, night and total ‘as needed’ use will be analysed using separate models, following the same modelling method. Change from baseline will be calculated as the difference between the mean of all days during the randomised treatment period and the mean of all days during the last 10 days of the run-in period.

The ANCOVA models will include randomised treatment, pre-study treatment and region as categorical factors and baseline ‘as needed’ medication use as a continuous covariate. Baseline ‘as needed’ medication use definition is specified in Section 3.1.1. Least squared means by randomised treatment group and differences in least squared means (between randomised treatment groups) along with corresponding 95% CIs will be estimated.

The percentage of controller use days will be analysed using descriptive statistics by treatment, and modelled through an ANCOVA model with randomised treatment, pre-study treatment and region as factors.

Summary statistics for ‘as needed’ free days (%) and change from baseline in ‘as needed’ free days (%) will be produced by treatment. The change from baseline in ‘as needed’ free days (%) will be analysed using an ANCOVA model with randomised treatment, pre-study treatment and region as categorical factors and baseline ‘as needed’ free days (%) as a continuous covariate. Baseline ‘as needed’ free days (%) definition is specified in Section 3.1.1.

4.2.6.8 Maintenance medication compliance

Summary statistics about maintenance medication compliance will be produced. See Section 3.6.3 for metrics. To examine changes in compliance over time the proportion of days where patients used ≥ 1 inhalation will be plotted over the randomised treatment period by week. Mean maintenance medication use per day will be depicted graphically by week and treatment.

4.2.7 Safety analysis

Safety variables will be presented descriptively by actual given treatment and pre-study treatment; no formal statistical hypothesis testing will be conducted.

The following safety variables will be summarised by treatment:

- Vital signs (pulse rate, systolic blood pressure, diastolic blood pressure)
 - Raw measurements (Visits 2, 6 and end of treatment)
 - Change from baseline (Visit 2 to end of treatment)
- Physical examination (general appearance, respiratory, cardiovascular, abdomen, head/neck)
 - Shift tables from baseline to the end of treatment

A summary overview table of patients with adverse events, with fatal adverse events, SAEs, DAEs and OAEs during the randomised treatment period will be presented by treatment, and by treatment and pre-study treatment.

The number and percentage of patients who experience one or more AE during run-in, and follow-up will be tabulated by SOC and PT and by treatment. The incidence rate of AEs will also be presented in the tables. The incidence rate is defined as the number of patients who have experienced the event per 100 patient treatment years.

The number and percentage of patients who experience one or more AE/SAE/DAE over the randomised treatment will be tabulated by SOC and PT by treatment and by treatment and pre-study treatment. The incidence rate of AEs will also be presented in the tables. The number of percentage of patients who experience common AEs (frequency of $\geq 2\%$) common SAEs (frequency of $\geq 0.2\%$), and common DAE (frequency of $\geq 0.2\%$) will be summarised by preferred term and treatment. In addition, summary tables of AEs representing potential β_2 agonist effects and AEs representing potential ICS effects will be produced by medical concept and preferred term and by treatment.

The number of events and event rates for AEs and SAEs will also be presented by SOC and PT by treatment. Event rates are defined as the total number of events across all patients in the treatment group per 100 patient treatment years.

The number and percentage of patients who experience a fatal AE during the randomised treatment will be tabulated by SOC and PT by treatment.

Patient information will be listed for those patients with SAEs, with DAE and with fatal AEs over the entire study period.

The number and percentage of patients experiencing other significant adverse events during the randomised treatment will be summarised by SOC and PT by treatment.

4.2.8 Supportive, subgroup, and sensitivity analyses

4.2.8.1 Supportive analysis

A supportive analysis will be carried out for the primary variable; annual severe exacerbation rate, to evaluate the non-inferiority hypothesis test by using a 97.5% 1 sided upper CI for the rate ratio. The annual exacerbation rates, the rate ratio and the corresponding 1-sided upper 97.5% CI for the rate ratio will be presented from the primary analysis model, excluding patients from France.

4.2.8.2 Subgroup analysis

For all subgroup analysis, if the model does not converge, then just summary statistics will be presented.

Pre-study treatment:

The treatment effect will be investigated in the 2 subgroups as defined by pre-study treatment to assess the consistency of the treatment effect across subgroups. An interaction effect will be evaluated for the following efficacy variables: severe exacerbation rate, time-to first severe exacerbation, ACQ, and FEV₁ pre- bronchodilator. For total inhaled steroid load, and time to asthma related discontinuation, descriptive statistics by treatment group will be presented by pre-study treatment category.

The treatment-by-pre-study treatment interaction term will be used to explore the consistency of the treatment effect across pre-study treatment subgroup categories in the below models. The interaction p-value from the Type III sums of squares test will be presented.

For severe exacerbation rate, and time-to first severe exacerbation, similar models to the overall population will be carried out but adding treatment-by-pre-study treatment interaction as factor into the model.

For ACQ, FEV₁ pre- bronchodilator, similar models to the overall population will be carried out but adding treatment-by-pre-study treatment, pre-study treatment-by-visit, and treatment-by-visit-by- pre-study treatment. The 3-way interaction will be used to estimate the least squares mean of the treatment effect and its corresponding 95% CI by visit. Forest plots presenting the overall and

pre-study treatment subgroup categories treatment effects and their associated 95% CI will be generated.

Severe asthma exacerbations:

For severe exacerbations rate, the consistency of treatment effect across subgroups will also be examined with regard to: sex, age, pre-study treatment, severe exacerbations 12 months prior to enrolment, baseline ACQ, asthma onset, smoking, region, baseline pre-bronchodilator FEV₁ PN, and average use of SABA during run-in period. This will be done by including a (subgroup*randomised treatment) interaction term in the models.

Forest plots presenting the rate ratios estimates and their associated 95% CI by subgroup: pre-study treatment category will be provided.

Subgroup analysis on exacerbations will not be conducted on an individual subgroup if less than 20 exacerbations were experienced in the respective subgroup.

Subgroups are described in **Table 2** below.

Table 2 Subgroups

Group	Subgroup
Pre-study treatment ^a	Uncontrolled on BD
	Controlled on ICS or LTRA
Sex	Male
	Female
Age	Adolescents: 12-<18 years
	Adults: 18 - <65 years
	Elderly: ≥65 years
Severe exacerbations 12 months prior to enrolment ^b	0
	≥1
Baseline ACQ	≤0.75
	>0.75 - ≤1.5
	>1.5
Asthma onset	New diagnosis: Asthma diagnosed in the last 2 years.
	Not new diagnosis: Asthma diagnosed over 2 years ago.
Smoking	Never
	Current/Former
Region ^c	Latin America
	EU
	East Asia
	Rest of World
FEV1 %PN Pre bronchodilator (run-in)	<80
	≥80 to <100
	≥ 100
Average use of SABA per day during run-in period (puffs)	0 to < 1
	1 to 2
	> 2

^a Uncontrolled on BD: Uncontrolled on an inhaled short-acting BD 'as needed' (SABA and/or short-acting anticholinergic agent); Controlled on ICS or LTRA: Controlled on mono-maintenance therapy with either a low dose ICS or a LTRA in addition to 'as needed' use of inhaled short-acting BD (SABA and/or short-acting anticholinergic agent).

^b Severe exacerbation definition at baseline is different to the study definition.

^c See Section 3.1 for a list of countries in each region.

4.2.8.3 Sensitivity analysis

Sensitivity analyses of the primary variable will be carried out to assess the robustness of the treatment effect under different underlying assumptions for missingness.

Severe asthma exacerbations will be analysed by the same Negative binomial regression model as described in Section 4.2.5.1, with only difference that any exacerbations occurring after discontinuation of randomised study drug will be accounted for in the analysis, and offset for adjustment of a patient's follow-up time will be accounted for as the time from first dose of IP and up to study discontinuation, regardless of whether patient pre-maturely discontinued randomised study drug or not, see Section 3.4.1.2.

Similarly, to the primary analysis described in Section 4.2.5.1, the Negative Binomial regression will be fitted twice to the data:

The first analysis will evaluate the non-inferiority hypothesis test by including data also after IP discontinuation, but excluding patients from France. From this analysis the annual exacerbation rates, the rate ratio and the corresponding 1-sided upper 95% CI for the rate ratio will be presented.

The second analysis will evaluate the superiority hypothesis by including all data, regardless of pre-maturely IP discontinuation. From this analysis the annual exacerbation rates, the rate ratio and the corresponding 2-sided 95% CI for the rate ratio and p-value will be presented.

In addition, a sensitivity analysis assuming MNAR will be carried out.

The same approach will be used for this sensitivity analysis, that is, the Negative binomial regression model will be fitted twice to data, where:

The first analysis will evaluate the consistency in the primary endpoint and the non-inferiority hypothesis test by assuming data after IP discontinuation to be MNAR, but excluding patients from France. From this analysis the annual exacerbation rates, the rate ratio and the corresponding 1-sided upper 95% CI for the rate ratio will be presented.

The second analysis will evaluate the consistency in the primary endpoint and the superiority hypothesis by assuming data after IP discontinuation to be MNAR. From this analysis the annual exacerbation rates, the rate ratio and the corresponding 2-sided 95% CI for the rate ratio and p-value will be presented

For MNAR (both analyses), a 'Jump to Reference' (J2R) approach will be used, where post-IP discontinuation data will be imputed for both treatment arms based on the estimated rate observed in the control arm before IP-discontinuation.

The controlled imputation method was introduced by [Keene et al, 2014](#) and further developed at AstraZeneca [[Wan et al, 2015](#), [Gottlow et al, 2015](#)], and allows for different underlying assumptions to be used. As with the primary analysis this sensitivity analysis includes all data until patients discontinue IP.

For this method, an underlying negative binomial stochastic process for the rate of exacerbations is assumed and post-IP discontinuation counts will be imputed conditional upon the observed number of events prior to IP discontinuation.

The method involves first fitting the primary analysis i.e. negative binomial regression model to the observed data and then imputing post-IP discontinuation counts by sampling from the conditional negative binomial probability relating post-IP discontinuation counts and observed prior-IP discontinuation counts.

$$Pr(Y_{ij,2} = y_2 | Y_{ij,1} = y_1) = \frac{\Gamma(\gamma + y_1 + y_2)}{\Gamma(y_2 + 1)\Gamma(\gamma + y_1)} p_j^{y_2} (1 - p_j)^{\gamma + y_1} \quad (1)$$

Here y_1 is number of counts before IP discontinuation, y_2 is number of counts after IP discontinuation, γ is the dispersion parameter and which is assumed to be the same for different treatment arms, j denotes the treatment arm and i denotes the subject identifier.

Furthermore

$$p_j = \frac{p_{j,2} - p_{j,1}p_{j,2}}{1 - p_{j,1}p_{j,2}} \quad (2)$$

where $p_{j,1}$ is the estimated negative binomial distribution rate parameter before IP discontinuation from the study, and $p_{j,2}$ is the rate parameter after IP discontinuation. For J2R, $p_{j,2}$ will be equal to $p_{2,1}$ (with adjustment of duration of time) where $p_{2,1}$ is the estimated rate parameter for the Pulmicort bid group up to IP discontinuation.

The imputed number of exacerbations that would have been seen is then combined with the observed exacerbations and data are analysed using the primary analysis method, i.e. by the same Negative binomial regression model as described in Section 4.2.5.1.

This analysis is repeated multiple times and the results combined using Rubin's formulae [Rubin, 1987]. For those patients who discontinue IP during study period, the total time at risk of an exacerbation (observed + imputed) will be 365 days. A seed of 784088 will be used and 100 imputations will be carried out.

4.2.9 Exploratory analysis

Descriptive reporting of the resource utilization data and health related quality of life data based on the EQ-5D-5L will be presented in the CSR. The data will be combined with economic data collected independently of the study to construct comparative health economic analyses between treatment groups. The economic analyses and cost-effectiveness analyses that include data external to the study will be reported in a separate health economic report and will not be included in the CSR.

Baseline is calculated as described in Section 3.1.1. End of treatment is calculated as described in Section 3.1.2.

4.2.9.1 Health care resource utilization and work and school absence

Descriptive statistics by treatment will be presented for asthma related health care utilisation variables.

At baseline and at subsequent treatment visits until EoT, the patient will be asked questions about asthma-related health care resource use (HRU) events since last visit as well as asthma-related sickness and absence from work or education.

The patient will be asked about health care resource use in terms of:

- Hospitalizations (Number of days)
 - Hospitalization intensive care unit (ICU)
 - Hospitalization general ward (GW)
- ER visits
- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids.
- Ambulance transport (number)
- Specialist visit
- Primary health care physician visit
- Other health care visit
- Home visits physician
- Home visits other health care
- Telephone calls physician
- Telephone calls nurse

HRU will be asthma-related only. Descriptive statistics will be presented for each health care resource item, by treatment group. Summary measures to be included are total number of each HRU event (visits) and/or days of events, number and percentage of patients experiencing at least one HRU event, and the total number of each HRU event or days of event divided by patient treatment years (annual rate).

The patient will be asked about work and school productivity loss in terms of:

- Work absence due to your asthma (days)

- School absence due to asthma (days)

Descriptive statistics will be presented for work and school absence, by treatment group. Summary measures to be included are total number of days, number and percentage of patients experiencing at least one absence day, and mean number of days absent per patient per year.

4.2.9.2 EQ-5D-5L

Summary statistics by treatment will be provided for absolute and change from baseline values in EQ-5D-5L (VAS and index) by treatment and visit. Boxplots will be produced to show the absolute values at baseline and each visit. Further, EQ-5D-5L domains will be described by treatment and visit.

The EQ-5D-5L consists of 2 pages - the EQ-5D descriptive system and the VAS. The descriptive system comprises five dimensions, mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each dimension has five levels (response options): no problems, slight problems, moderate problems, severe problems and extreme problems. The VAS records the respondent's self-rated health on a 20cm vertical visual analogue scale with endpoints labelled "the best health you can imagine" and "the worst health you can imagine".

The questions will be assessed at baseline and at subsequent treatment visits until EoT.

EQ-5D will be presented in three different ways:

- 1) Presenting results from the EQ-5D-5L descriptive system as a health profile at baseline, all post-baseline visits and EoT (% , n) by domain
- 2) Presenting results of the VAS as a measure of overall self-rated health status - baseline scores, scores at each visit, changes from baseline at each visit and boxplots of VAS score over the randomised treatment period
- 3) Presenting results from the EQ-5D-5L crosswalk index value (using UK value set, see below) baseline utility, each visit, changes from baseline at each visit and boxplots of utility over the randomised treatment period

The National Institute of Health and Care Excellence (NICE) in England has made an interim position statement (August 2017) about the use of the 5 level version of the EQ-5D for companies, academic groups, and others preparing evidence submissions for NICE.

The main recommendations are:

If the 5 level is used (EQ-5D-5L), then apply the mapping function developed by [Van Hout et al, 2012](#)

to convert it to the EQ-5D-3L for the reference-case analyses

SAS syntax for computing EQ-5D-5L crosswalk index values with SAS using the United Kingdom (UK) value set can be found in [Appendix 5](#): .

No imputation will be made for missing data in either the EQ-5D-5L or VAS responses.

5. CHANGES OF ANALYSIS FROM PROTOCOL

Decision to exclude 12 randomised patients from study site 5702 (Poland) will be excluded from the Full Analysis set and the Safety analysis set due to significant deviations. The deviations were mainly relating to unavailability, discrepancies and poor quality of source data which question the validity and integrity of the trial data generated from this site. Data listings for these 12 patients will be provided in Appendix 12.2 in CSR.

Decision made to exclude all randomised patients in France in the non-inferiority test due to Ethic Committee rejection of CSP amendment 4 in France.

Decision to exclude 1 randomised patient from study site 2612 (Germany) that was randomised in error from Full Analysis Set and Safety Analysis Set. Due to the subject age, local ethics committee decided data of this patient cannot be used for the analysis. As patient signed informed consent, data listings will be provided for this patient in Appendix 12.2 in CSR.

6. REFERENCES

Bateman et al 2004

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels R, et al (2004) Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control (GOAL) study. *Am J Respir Crit Care Med*, 170:836-44.

Friede and Schmidli, 2010

Friede T and Schmidli H. Blinded sample size reestimation with negative binomial counts in superiority and non-inferiority trials. *Methods Inf Med*. 2010;49(6):618-24. doi: 10.3414/ME09-02-0060. Epub 2010 Aug 5.

Gottlow et al, 2015

Gottlow M, Hollis S, Wan R, Hirsch I, Darilay A, Weissfeld L, France L. A Simulation study of a controlled imputation approach for analyzing missing data in recurrent events due to early discontinuations. *PSI Annual Conference 2015*.

Van Hout et al, 2012

Van Hout B, Janssen M.F, Feng Y.S, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard A.S. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets: *VALUE IN HEALTH* 15. 2012; 708 –715

Keene et al 2007

Keene ON, Jones MRK, Lane PW, Anderson J. Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. *Pharmaceutical Statistics* 2007;6:89–97.

Keene et al, 2014

Keene, O. N., Roger, J. H., Hartley, B. F. and Kenward, M. G. (2014), Missing data sensitivity analysis for recurrent event data using controlled imputation. *Pharmaceut. Statist.*, 13: 258–264.

Kenward and Roger 1997

Kenward MG and Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 1997; 53: 983–997.

Pauwels et al 2003

Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV et al, on behalf of the START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361:1071-6.

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Quanjer et al 2012

Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40(6):1324-43.

Rubin, 1987

Rubin DB. *Multiple imputation for nonresponse in surveys*. New York: John Wiley & Sons, Inc. 1987.

Wan et al, 2015

Wan R, Hirsch I, Gottlow M, Hollis S, Darilay A, Weissfeld L, France L. Controlled imputation approach for analyzing missing data in recurrent events due to early discontinuations. *DIA/FDA Statistics Forum* 2015.

7. APPENDIX 1: METHOD FOR CALCULATING PREDICTED NORMAL FEV1

7.1 Equation for calculating predicted multi-ethnic predicted normal FEV1

The equation for calculating predicted normal FEV₁ is of the form:

$$PN\ FEV_1 = \exp(a_0 + a_1 \cdot \ln(\text{Height}) + a_2 \cdot \ln(\text{Age}) + a_3 \cdot \text{AfrAm} + a_4 \cdot \text{NEAsia} + a_5 \cdot \text{SEAsia} + a_6 \cdot \text{Other} + M_{\text{spline}})$$

The following input variables are used in the predicted normal FEV₁ equation:

- *Height* is the patient's height in cm (to the nearest 0.1 cm)
- *Age* is the patient's age in years (to the nearest 0.1 years) – this should be recalculated based on the visit date and patient's date of birth
- *AfrAm* is equal to 1 if the patient's ethnic population is African American, 0 otherwise
- *NEAsia* is equal to 1 if the patient's ethnic population is North East Asian, 0 otherwise
- *SEAsia* is equal to 1 if the patient's ethnic population is South East Asian, 0 otherwise
- *Other* is equal to 1 if the patient's ethnic population is Other/Mixed, 0 otherwise

The constants a_0 , a_1 , a_2 , a_3 , a_4 and a_5 depend on the patient's sex, as outlined in the table below:

Constant	Males	Females
a0	-10.3420	-9.6987
a1	2.2196	2.1211
a2	0.0574	-0.0270
a3	-0.1589	-0.1484
a4	-0.0351	-0.0149
a5	-0.0881	-0.1208
a6	-0.0708	-0.0708

The final term in the predicted normal FEV₁ equation, M_{spline} , is obtained a lookup table (see Section 7.2), based on the patient's age and sex.

For patients aged 25 or over, the following equation may be used to approximate M_{spline} in place of the lookup tables:

$$M_{\text{spline}} = b_0 + b_1 \cdot (\text{Age}/100) + b_2 \cdot (\text{Age}/100)^2 + b_3 \cdot (\text{Age}/100)^3 + b_4 \cdot (\text{Age}/100)^4 + b_5 \cdot (\text{Age}/100)^5$$

where b_0 , b_1 , b_2 , b_3 , b_4 and b_5 are constants that depend on the patient's sex, as outlined in the table below:

Constant	Males	Females
b0	0.3901	0.0552
b1	-1.0579	1.6029
b2	1.4743	-6.4845
b3	-2.1077	10.2723
b4	-0.1215	-9.8630
b5	0.8873	3.8802

7.2 Lookup table for final term

The following lookup table is used for determining the value of M_{spline} in the equation for calculating predicted normal FEV₁ (see Section 3.4.6). For ages other than those listed here, the value is derived using linear interpolation of the two nearest ages (i.e. those ages either side of the patient's actual age).

The lookup table is available from the Global Lung Function Initiative website (URL at the time of writing: <http://www.lungfunction.org/files/lookuptables7April2013.xls>).

Age	Male	Female	Age	Male	Female	Age	Male	Female
12	-0.0176	0.0274	20.5	0.2090	0.1842	29	0.1574	0.1625
12.25	-0.0101	0.0386	20.75	0.2092	0.1842	29.25	0.1554	0.1617
12.5	-0.0019	0.0496	21	0.2091	0.1841	29.5	0.1534	0.1608
12.75	0.0071	0.0604	21.25	0.2089	0.1840	29.75	0.1514	0.1599
13	0.0169	0.0709	21.5	0.2084	0.1838	30	0.1495	0.1590
13.25	0.0274	0.0810	21.75	0.2079	0.1835	30.25	0.1475	0.1581
13.5	0.0384	0.0907	22	0.2071	0.1832	30.5	0.1455	0.1572
13.75	0.0497	0.0999	22.25	0.2063	0.1828	30.75	0.1436	0.1562
14	0.0612	0.1086	22.5	0.2053	0.1823	31	0.1417	0.1553
14.25	0.0728	0.1168	22.75	0.2042	0.1818	31.25	0.1397	0.1543
14.5	0.0844	0.1244	23	0.2030	0.1812	31.5	0.1378	0.1533
14.75	0.0958	0.1315	23.25	0.2016	0.1806	31.75	0.1359	0.1523
15	0.1068	0.1379	23.5	0.2002	0.1799	32	0.1340	0.1512
15.25	0.1175	0.1438	23.75	0.1987	0.1792	32.25	0.1321	0.1501
15.5	0.1276	0.1492	24	0.1970	0.1785	32.5	0.1302	0.1490
15.75	0.1371	0.1540	24.25	0.1954	0.1777	32.75	0.1283	0.1479
16	0.1460	0.1583	24.5	0.1936	0.1769	33	0.1265	0.1467
16.25	0.1542	0.1621	24.75	0.1918	0.1761	33.25	0.1246	0.1456
16.5	0.1616	0.1655	25	0.1899	0.1753	33.5	0.1227	0.1444
16.75	0.1684	0.1684	25.25	0.1880	0.1745	33.75	0.1209	0.1431
17	0.1744	0.1711	25.5	0.1861	0.1737	34	0.1190	0.1418
17.25	0.1798	0.1733	25.75	0.1841	0.1729	34.25	0.1172	0.1406
17.5	0.1845	0.1753	26	0.1821	0.1721	34.5	0.1153	0.1392
17.75	0.1887	0.1770	26.25	0.1801	0.1713	34.75	0.1135	0.1379
18	0.1924	0.1785	26.5	0.1781	0.1705	35	0.1116	0.1365
18.25	0.1956	0.1797	26.75	0.1760	0.1697	35.25	0.1097	0.1351
18.5	0.1984	0.1808	27	0.1739	0.1690	35.5	0.1078	0.1337
18.75	0.2008	0.1816	27.25	0.1718	0.1682	35.75	0.1059	0.1322
19	0.2029	0.1823	27.5	0.1697	0.1674	36	0.1040	0.1308
19.25	0.2046	0.1829	27.75	0.1677	0.1666	36.25	0.1021	0.1292
19.5	0.2060	0.1833	28	0.1656	0.1658	36.5	0.1001	0.1277
19.75	0.2072	0.1837	28.25	0.1635	0.1650	36.75	0.0982	0.1262
20	0.2081	0.1839	28.5	0.1615	0.1642	37	0.0962	0.1246
20.25	0.2087	0.1841	28.75	0.1594	0.1634	37.25	0.0943	0.1230

Age	Male	Female
37.5	0.0923	0.1214
37.75	0.0903	0.1197
38	0.0883	0.1180
38.25	0.0863	0.1164
38.5	0.0843	0.1147
38.75	0.0823	0.1129
39	0.0803	0.1112
39.25	0.0782	0.1094
39.5	0.0762	0.1076
39.75	0.0742	0.1058
40	0.0721	0.1040
40.25	0.0700	0.1022
40.5	0.0680	0.1003
40.75	0.0659	0.0985
41	0.0638	0.0966
41.25	0.0617	0.0947
41.5	0.0596	0.0928
41.75	0.0575	0.0909
42	0.0554	0.0889
42.25	0.0533	0.0870
42.5	0.0511	0.0850
42.75	0.0490	0.0830
43	0.0469	0.0811
43.25	0.0448	0.0791
43.5	0.0427	0.0771
43.75	0.0406	0.0751
44	0.0386	0.0731
44.25	0.0365	0.0710
44.5	0.0344	0.0690
44.75	0.0323	0.0670
45	0.0302	0.0650
45.25	0.0281	0.0630
45.5	0.0261	0.0609
45.75	0.0240	0.0589
46	0.0219	0.0568
46.25	0.0198	0.0548
46.5	0.0177	0.0527

Age	Male	Female
47	0.0135	0.0486
47.25	0.0114	0.0465
47.5	0.0093	0.0445
47.75	0.0072	0.0424
48	0.0050	0.0403
48.25	0.0029	0.0382
48.5	0.0007	0.0361
48.75	-0.0015	0.0339
49	-0.0036	0.0318
49.25	-0.0058	0.0297
49.5	-0.0080	0.0275
49.75	-0.0103	0.0254
50	-0.0125	0.0232
50.25	-0.0147	0.0210
50.5	-0.0170	0.0188
50.75	-0.0193	0.0166
51	-0.0216	0.0144
51.25	-0.0239	0.0122
51.5	-0.0262	0.0099
51.75	-0.0285	0.0077
52	-0.0309	0.0054
52.25	-0.0332	0.0032
52.5	-0.0356	0.0009
52.75	-0.0380	-0.0014
53	-0.0404	-0.0037
53.25	-0.0428	-0.0061
53.5	-0.0453	-0.0084
53.75	-0.0478	-0.0108
54	-0.0502	-0.0131
54.25	-0.0527	-0.0155
54.5	-0.0552	-0.0179
54.75	-0.0578	-0.0203
55	-0.0603	-0.0227
55.25	-0.0629	-0.0252
55.5	-0.0654	-0.0276
55.75	-0.0680	-0.0301
56	-0.0706	-0.0326

Age	Male	Female
56.5	-0.0759	-0.0375
56.75	-0.0785	-0.0401
57	-0.0812	-0.0426
57.25	-0.0839	-0.0451
57.5	-0.0866	-0.0477
57.75	-0.0893	-0.0503
58	-0.0920	-0.0529
58.25	-0.0947	-0.0555
58.5	-0.0975	-0.0581
58.75	-0.1002	-0.0607
59	-0.1030	-0.0634
59.25	-0.1058	-0.0660
59.5	-0.1086	-0.0687
59.75	-0.1114	-0.0714
60	-0.1143	-0.0741
60.25	-0.1171	-0.0768
60.5	-0.1199	-0.0795
60.75	-0.1228	-0.0822
61	-0.1257	-0.0850
61.25	-0.1286	-0.0878
61.5	-0.1315	-0.0905
61.75	-0.1344	-0.0933
62	-0.1373	-0.0961
62.25	-0.1402	-0.0989
62.5	-0.1431	-0.1018
62.75	-0.1461	-0.1046
63	-0.1490	-0.1075
63.25	-0.1519	-0.1103
63.5	-0.1549	-0.1132
63.75	-0.1578	-0.1161
64	-0.1608	-0.1190
64.25	-0.1638	-0.1219
64.5	-0.1667	-0.1249
64.75	-0.1697	-0.1278
65	-0.1727	-0.1308
65.25	-0.1757	-0.1338
65.5	-0.1786	-0.1368

8. APPENDIX 2: IDENTIFICATION OF ADDITIONAL STEROID

66.25	-0.1876	-0.1458	75.75	-0.3018	-0.2674	85.25	-0.4092	-0.3883
66.5	-0.1906	-0.1488	76	-0.3048	-0.2707	85.5	-0.4119	-0.3913
66.75	-0.1936	-0.1519	76.25	-0.3077	-0.2740	85.75	-0.4145	-0.3944
67	-0.1966	-0.1550	76.5	-0.3107	-0.2773	86	-0.4172	-0.3974
67.25	-0.1996	-0.1580	76.75	-0.3136	-0.2805	86.25	-0.4198	-0.4004
67.5	-0.2026	-0.1611	77	-0.3166	-0.2838	86.5	-0.4225	-0.4034
67.75	-0.2056	-0.1642	77.25	-0.3195	-0.2871	86.75	-0.4251	-0.4064
68	-0.2086	-0.1674	77.5	-0.3224	-0.2903	87	-0.4277	-0.4094
68.25	-0.2116	-0.1705	77.75	-0.3253	-0.2936	87.25	-0.4303	-0.4124
68.5	-0.2147	-0.1736	78	-0.3282	-0.2968	87.5	-0.4329	-0.4153
68.75	-0.2177	-0.1768	78.25	-0.3311	-0.3001	87.75	-0.4355	-0.4183
69	-0.2207	-0.1799	78.5	-0.3340	-0.3033	88	-0.4381	-0.4213
69.25	-0.2237	-0.1831	78.75	-0.3369	-0.3065	88.25	-0.4407	-0.4242
69.5	-0.2267	-0.1863	79	-0.3398	-0.3098	88.5	-0.4433	-0.4272
69.75	-0.2298	-0.1895	79.25	-0.3427	-0.3130	88.75	-0.4459	-0.4301
70	-0.2328	-0.1926	79.5	-0.3455	-0.3162	89	-0.4484	-0.4330
70.25	-0.2358	-0.1958	79.75	-0.3484	-0.3194	89.25	-0.4510	-0.4359
70.5	-0.2388	-0.1991	80	-0.3512	-0.3226	89.5	-0.4536	-0.4389
70.75	-0.2418	-0.2023	80.25	-0.3541	-0.3258	89.75	-0.4561	-0.4418
71	-0.2449	-0.2055	80.5	-0.3569	-0.3290	90	-0.4586	-0.4446
71.25	-0.2479	-0.2087	80.75	-0.3597	-0.3322	90.25	-0.4612	-0.4475
71.5	-0.2509	-0.2120	81	-0.3625	-0.3354	90.5	-0.4637	-0.4504
71.75	-0.2539	-0.2152	81.25	-0.3654	-0.3386	90.75	-0.4662	-0.4533
72	-0.2569	-0.2184	81.5	-0.3682	-0.3417	91	-0.4687	-0.4561
72.25	-0.2599	-0.2217	81.75	-0.3709	-0.3449	91.25	-0.4712	-0.4590
72.5	-0.2630	-0.2249	82	-0.3737	-0.3480	91.5	-0.4737	-0.4618
72.75	-0.2660	-0.2282	82.25	-0.3765	-0.3512	91.75	-0.4762	-0.4647
73	-0.2690	-0.2315	82.5	-0.3793	-0.3543	92	-0.4787	-0.4675
73.25	-0.2720	-0.2347	82.75	-0.3820	-0.3574	92.25	-0.4811	-0.4703
73.5	-0.2750	-0.2380	83	-0.3848	-0.3606	92.5	-0.4836	-0.4732
73.75	-0.2780	-0.2413	83.25	-0.3875	-0.3637	92.75	-0.4861	-0.4760
74	-0.2810	-0.2445	83.5	-0.3903	-0.3668	93	-0.4885	-0.4788
74.25	-0.2840	-0.2478	83.75	-0.3930	-0.3699	93.25	-0.4910	-0.4816
74.5	-0.2869	-0.2511	84	-0.3957	-0.3730	93.5	-0.4934	-0.4844
74.75	-0.2899	-0.2543	84.25	-0.3984	-0.3760	93.75	-0.4959	-0.4871
75	-0.2929	-0.2576	84.5	-0.4011	-0.3791	94	-0.4983	-0.4899
75.25	-0.2959	-0.2609	84.75	-0.4038	-0.3822	94.25	-0.5007	-0.4927

MEDICATIONS FOR ANALYSES

Relevant SAP section	Parameter	Source of data
3.4.3	Additional steroids for asthma*	<p>1a. Inhaled corticosteroids as recorded on the EXACASI module</p> <p>1b. MED module with ATC codes R03BA or R03AK and reason is either 'Disease under study' or 'Protocol defined exacerbation of disease under study'.</p> <p>1c. MED module with ATC codes R03BA or R03AK and Therapy reason is 'Adverse event' and Reason for therapy text in the MED module contains the word 'asthma' or 'astma'. (Note each letter in asthma/astma should be allowed to be in upper/lower case)</p> <p>1d. MED module with ATC codes R03BA or R03AK and Therapy reason is 'Other' and Reason for therapy contains the word 'asthma' or 'astma' (Note each letter in asthma/astma should be allowed to be in upper/lower case)</p> <p>2. Systemic corticosteroids given for an exacerbation as per the EXACASI module</p> <p>3a. Systemic corticosteroids recorded on the MED module where ATC code is H02AB and Therapy reason is 'Disease under study' or 'Protocol defined exacerbation of disease under study'</p> <p>3b. Systemic corticosteroids recorded on the MED module where ATC code is H02AB and Therapy reason is 'Adverse event' and Reason for therapy text in the MED module contains the word 'asthma' or 'astma'. (Note each letter in asthma/astma should be allowed to be in upper/lower case)</p> <p>3c. Systemic corticosteroids recorded on the MED module where ATC code is H02AB and Therapy reason is 'Other' and Reason for therapy text contains the word 'asthma' (Note each letter in asthma/astma should be allowed to be in upper/lower case)</p>
3.4.3	Total inhaled steroid load**	1a and any medication in the MED module with ATC code either R03BA or R03AK (all reasons) plus investigational product. The exception is on the treatment end date, when only those steroids prescribed for asthma (1a above) are used.
3.4.4	Number of days of systemic GCS use due to asthma***	2, 3a, 3b, or 3c above

* For medications starting on the day of IP discontinuation, the only sources of data are 1a, 2 and 3a

** For medications starting on the day of IP discontinuation, the only source of data is 1a

*** For medications starting on the day of IP discontinuation, the only sources of data are 2 and 3a.

9. APPENDIX 3: POTENTIAL CLASS EFFECTS B2-AGONISTS AND POTENTIAL ICS EFFECTS

The following is a list of preferred terms, in MedDRA version 20.0, representing potential β_2 -agonist effects, presented by medical concept (group of terms describing the same medical phenomenon). The preferred terms and the medical concepts have been defined by AstraZeneca and is applicable for the Symbicort development program as needed.

Potential class effects β_2 - agonists	
<i>Medical concept</i>	<i>MedDRA (version 20.0) Preferred Term</i>
Agitation	Agitation Aggression
Anxiety	Anxiety Feeling jittery Nervousness Restlessness Tension
Hyperglycaemia	Blood glucose increased Hyperglycaemia
Headache	Headache
Muscle cramp	Muscle spasms
Hypokalaemia	Blood Potassium decreased Hypokalaemia
Sleep effects	Initial insomnia Insomnia Sleep disorder
Tremor	Tremor
Cardiac events	Acute myocardial infarction Adams-Stokes syndrome Angina pectoris Angina unstable Arrhythmia Arrhythmia supraventricular Atrial fibrillation Atrial flutter Atrial tachycardia Blood pressure ambulatory increased Blood pressure increased

Blood pressure systolic increased Extrasystoles Heart rate increased Hypertension Palpitations Sinus tachycardia Supraventricular extrasystoles Supraventricular tachyarrhythmia Supraventricular tachycardia Tachyarrhythmia Tachycardia Ventricular extrasystoles
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Choice of terms agreed between Symbicort's GSP Ulrika Larsdotter, SP Fredrik Randers, SSAMT leader Svante Joelson and PS Ulrika Emerath on 28 April 2017.

The following list is of preferred terms, in MedDRA version 20.0, representing potential ICS effects, presented by location and medical concept (group of terms describing the same medical phenomenon). The preferred terms and the medical concepts have been defined by AstraZeneca and is applicable for the Symbicort development program as needed.

Potential Class effects		
Inhaled corticosteroids		
<i>Location</i>	<i>Medical concept</i>	<i>MedDRA (version 20.0) Preferred Term</i>
Local steroid effects	Candidiasis	Candida infection
		Oral candidiasis
		Oropharyngeal candidiasis
	Voice effects	Aphonia
		Dysphonia
Systemic steroid effects	Adrenal suppression	Addison's disease
		Adrenal insufficiency
		Adrenal suppression
		Adrenocortical insufficiency acute
		Blood cortisol decreased
		Cortisol free urine decreased
		Secondary adrenocortical insufficiency
		Urine cortisol/creatinine ratio decreased
	Diabetes control	Diabetes mellitus
		Diabetes mellitus inadequate control
	Metabolic bone	All Pts in MedDRA Standardised

effects and fractures	MedDRA query (SMQ): Osteoporosis/osteopenia, version 20.0 broad
Growth retardation	Growth retardation Body height below normal Body height decreased
Ocular effects	Cataract Cataract cortical Cataract diabetic Cataract nuclear Cataract subcapsular Glaucoma Angle closure glaucoma Open angle glaucoma Intraocular pressure increased Lenticular opacities Ocular hypertension Glaucomatous optic disc atrophy Intraocular pressure test abnormal
Psychiatric effects	Depressed mood Depressive symptom Dysphoria Euphoric mood Insomnia Psychotic disorder Restlessness
Skin effects	Contusion Ecchymosis Increased tendency to bruise Petechiae Purpura Skin atrophy
Taste effects	Dysgeusia

Choice of terms agreed between Symbicort's GSP Ulrika Larsdotter, SP Fredrik Randers, SSAMT leader Svante Joelson and PS Ulrika Emerath on 28 April 2017.
 Updated to MedDRA 20.0 by Ulrika Emerath on 4 May 2017.

10. APPENDIX 4: VISIT WINDOWING

Visit windowing for run-in, on-treatment and end of treatment measurements will be conducted for FEV₁, FVC, ACQ, AQLQ, EQ5D, vital signs, height, weight and physical examination. For each measurement, the available data will be used to determine which analysis visit number the measurement belongs to. Raw visit numbers will not be used in analysis. For each analysis visit the acceptable timing range describes the earliest and latest date a measurement can occur to be considered as the value for that analysis visit. For instance, the acceptable timing range for analysis visit 4 is >13 to 21 weeks, so measurements occurring on or before 13 weeks and after 21 weeks cannot be considered as an analysis Visit 4 measurement.

Table 3 Acceptable timing range for each visit

Stage	Analysis Visit number	Timepoint	Endpoints collected	Acceptable time range in relation to first dose of IP
Run-in	Visit 2	-	FEV ₁ , FVC, ACQ, AQLQ	FEV ₁ , FVC, ACQ, AQLQ: Visit 2 measurement from date of Visit 2 until the day of first run-in medication. Vital signs, height weight and physical examination: Visit 2
Baseline visit	Visit 3	0 weeks	FEV ₁ , FVC, ACQ, AQLQ, EQ5D	See Section 3.1.1 for definitions of baseline.
On treatment*	Visit 4	17 weeks	FEV ₁ , FVC, ACQ, AQLQ, EQ5D	>13 to 21 weeks
On treatment*	Visit 5	34 weeks	FEV ₁ , FVC, ACQ, AQLQ, EQ5D	>30 to 38 weeks

On treatment	Visit 6	52 weeks	All, apart from height which is collected for adolescents only.	<p>≥48 weeks</p> <p>Acceptable upper range for measurements: FEV1, FVC: date of analysis Visit 6 and no later than the day after IP discontinuation.</p> <p>ACQ, AQLQ, EQ5D, vital signs, height (adolescents only), weight and physical examination: no later than 7 days after IP discontinuation.</p>
End of treatment	Visit 7	-	All, apart from height which is collected for adolescents only.	<p>End of treatment can occur anytime between Visit 3 and one day after IP discontinuation for all patients who took at least one dose of IP.</p> <p>Acceptable upper range for measurements: FEV1, FVC: date of analysis Visit 6 and no later than the day after IP discontinuation.</p> <p>ACQ, AQLQ, EQ5D, vital signs, height (adolescents only), weight and physical examination: no later than 7 days after IP discontinuation.</p>

*If a patient discontinues IP early, all measurements up to and including the day after IP discontinuation can be considered for on-treatment values.

Rules for FEV₁, FVC, EQ5D, vital signs, height, weight and physical examination:

1. Measurements from unscheduled visits (visit number with decimals of format X.0X or with a module occurrence number >1000) will not be used in the analysis. The rationale for this is that normally an unscheduled visit is made in connection to an asthma exacerbation or AE, and assessments at such visits will not be representative of scheduled visits. There are cases when a measurement cannot be completed at the scheduled visits. In these cases, the patient returns on another timepoint to complete the assessment. In these cases, the scheduled visit number is used in combination with a recording of the actual assessment date. Such an assessment will not be considered unscheduled and can be included in the analysis.
2. The order of selecting measurements for each visit is specified below. Visit timepoint is the CSP specified timepoint, as in CSP Table 1, i.e. Visit 4 timepoint is 4 weeks. Note that a scheduled visit inside another scheduled visit's timing window will be considered for analysis, e.g. a Visit 4 occurring in Visit 5 window (>30 - 38 weeks). Also note that if there is more than one non-missing observation at same date, the one

with the lowest module occurrence number should be used as that should be the original measurement. Refer to [Table 3](#) for acceptable timing range.

Rules for ACQ and AQLQ:

1. Unlike the other parameters, ACQ and AQLQ should not be measured on unscheduled visits in connection to for example an AE or exacerbation. Therefore, as visit numbers were not collected for ACQ and AQLQ, we only look at the assessment date in relation to the date of first dose of IP according to the acceptable timing range in [Table 3](#).
2. If there is more than one non-missing observation of ACQ and AQLQ at the same date the worse assessment should be used. Which assessment is worse is based on the total score. For ACQ a higher total score is worse, and for AQLQ a lower total score is worse.

Run-in analysis visit:

1. Use scheduled Visit 2 if available and within acceptable Visit 2 timing range. Include assessments *recorded* as Visit 2 even if before Visit 2 date and or after until day of run-in medication
2. If more than one scheduled Visit 2 in acceptable Visit 2 timing range use earliest scheduled visit.

Randomisation visit

1. If more than one scheduled Visit 3 in acceptable Visit 3 timing range use earliest scheduled visit.

On-treatment analysis Visits 4 and 5

1. Use closest scheduled visit to visit timepoint if within visit acceptable timing range and at most one day after IP discontinuation if patient is a non-completer. If 2 or more scheduled visits from visit timepoint are equidistant (and not more than 1 day after IP discontinuation if patient is a non-completer) use earlier visit.
2. Use closest other scheduled visit if within visit acceptable range and at most one day after IP discontinuation if patient is a non-completer. If 2 or more scheduled visits from visit timepoint are equidistant (and not more than 1 day after IP discontinuation if patient is a non-completer) use earlier visit.

End of treatment analysis visit for FEV₁ and FVC

If a Visit 6 measurement according to visit windows is missing, use last available non-missing measurement made at a scheduled visit but no later than one day after IP discontinuation.

End of treatment analysis visit for other variables

Other variables include ACQ, AQLQ, EQ5D, vital signs, height (adolescents only), weight and physical examination.

If a Visit 6 measurement according to visit windows is missing, use last available non-missing measurement made at a scheduled visit but no later than 7 days after IP discontinuation.

On-treatment analysis Visit 6

Patients must have completed at least 48 weeks on IP to have a Visit 6 measurement. For these patients, their Visit 6 measurements will be the same as their end of treatment measurements.

11. APPENDIX 5: COMPUTING EQ-5D-5L CROSSWALK INDEX VALUES WITH SAS USING THE UNITED KINGDOM (UK) VALUE SET

The variables for the 5 dimensions of the EQ-5D-5L descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'. If they are given different names the syntax code below will not work properly. The 5 variables should contain the values for the different dimensions in the EQ-5D health profile (i.e. 1, 2, 3, 4 or 5). The variable 'EQindex' contains the values of the EQ-5D-5L crosswalk index values on the basis of the UK set of weights.

You can copy and paste the syntax below directly into a SAS syntax window.

```
*****
*SAS syntax code for the computation of index*
*values with the UK TTO value set*
*****
data Euroqol.UK_tto;
set Euroqol.EQ5D_states;
EQindex = .;

if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=1) then EQindex = 1.000;
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=2) then EQindex = 0.879;
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=3) then EQindex = 0.848;
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=4) then EQindex = 0.635;
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=5) then EQindex = 0.414;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=1) then EQindex = 0.837;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=2) then EQindex = 0.768;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=3) then EQindex = 0.750;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=4) then EQindex = 0.537;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=5) then EQindex = 0.316;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=1) then EQindex = 0.796;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=2) then EQindex = 0.740;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=3) then EQindex = 0.725;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=4) then EQindex = 0.512;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=5) then EQindex = 0.291;
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=1) then EQindex = 0.584;
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=2) then EQindex = 0.527;
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=3) then EQindex = 0.513;
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=4) then EQindex = 0.352;
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=5) then EQindex = 0.186;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=1) then EQindex = 0.264;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=2) then EQindex = 0.208;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=3) then EQindex = 0.193;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=4) then EQindex = 0.112;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=5) then EQindex = 0.028;
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=1) then EQindex = 0.906;
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=2) then EQindex = 0.837;
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=3) then EQindex = 0.819;
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=4) then EQindex = 0.606;
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=5) then EQindex = 0.385;
if (mobility=1 and selfcare=1 and activity=2 and pain=2 and anxiety=1) then EQindex = 0.795;
if (mobility=1 and selfcare=1 and activity=2 and pain=2 and anxiety=2) then EQindex = 0.736;
if (mobility=1 and selfcare=1 and activity=2 and pain=2 and anxiety=3) then EQindex = 0.721;
if (mobility=1 and selfcare=1 and activity=2 and pain=2 and anxiety=4) then EQindex = 0.508;
if (mobility=1 and selfcare=1 and activity=2 and pain=2 and anxiety=5) then EQindex = 0.287;
if (mobility=1 and selfcare=1 and activity=2 and pain=3 and anxiety=1) then EQindex = 0.767;
```


if (mobility=5 and selfcare=5 and activity=4 and pain=3 and anxiety=2) then EQindex = -0.112;
if (mobility=5 and selfcare=5 and activity=4 and pain=3 and anxiety=3) then EQindex = -0.127;
if (mobility=5 and selfcare=5 and activity=4 and pain=3 and anxiety=4) then EQindex = -0.208;
if (mobility=5 and selfcare=5 and activity=4 and pain=3 and anxiety=5) then EQindex = -0.292;
if (mobility=5 and selfcare=5 and activity=4 and pain=4 and anxiety=1) then EQindex = -0.161;
if (mobility=5 and selfcare=5 and activity=4 and pain=4 and anxiety=2) then EQindex = -0.217;
if (mobility=5 and selfcare=5 and activity=4 and pain=4 and anxiety=3) then EQindex = -0.232;
if (mobility=5 and selfcare=5 and activity=4 and pain=4 and anxiety=4) then EQindex = -0.313;
if (mobility=5 and selfcare=5 and activity=4 and pain=4 and anxiety=5) then EQindex = -0.397;
if (mobility=5 and selfcare=5 and activity=4 and pain=5 and anxiety=1) then EQindex = -0.319;
if (mobility=5 and selfcare=5 and activity=4 and pain=5 and anxiety=2) then EQindex = -0.375;
if (mobility=5 and selfcare=5 and activity=4 and pain=5 and anxiety=3) then EQindex = -0.390;
if (mobility=5 and selfcare=5 and activity=4 and pain=5 and anxiety=4) then EQindex = -0.471;
if (mobility=5 and selfcare=5 and activity=4 and pain=5 and anxiety=5) then EQindex = -0.555;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=1) then EQindex = 0.028;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=2) then EQindex = -0.028;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=3) then EQindex = -0.043;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=4) then EQindex = -0.124;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=5) then EQindex = -0.208;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=1) then EQindex = -0.071;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=2) then EQindex = -0.127;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=3) then EQindex = -0.142;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=4) then EQindex = -0.223;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=5) then EQindex = -0.307;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=1) then EQindex = -0.095;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=2) then EQindex = -0.151;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=3) then EQindex = -0.166;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=4) then EQindex = -0.247;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=5) then EQindex = -0.331;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=1) then EQindex = -0.200;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=2) then EQindex = -0.256;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=3) then EQindex = -0.271;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=4) then EQindex = -0.352;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=5) then EQindex = -0.436;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=1) then EQindex = -0.358;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=2) then EQindex = -0.414;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=3) then EQindex = -0.429;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=4) then EQindex = -0.510;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=5) then EQindex = -0.594;

if (mobility = .) or (selfcare = .) or (activity = .) or (pain = .) or (anxiety = .) then EQindex = . ;

output;
run;